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New Substrates for Pauson-Khand Reaction

A Thesis Presented to the University of London
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the Degree of Doctor of Philosophy

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ABSTRACT

The Pauson-Khand reaction, a formal [2+2+1] cycloaddition of an alkene π bond, an alkyne π bond and carbon monoxide to form a five-membered ring, was discovered in the early 1970's.

This thesis presents the work undertaken towards the synthesis of two new types of substrates for this reaction; namely silicon tethered enynes and silyl enol ethers.

Silicon-tethered enynes as substrates for PKR

The scope of silicon-tethered Pauson-Khand reactions of vinylsilane and allylsilane derived enynes was fully explored. The vinylsilane derived enynes yielded monocyclopentenone where the carbons bound to the silicon tether were reduced during the course of the reaction. The allylsilane derived enynes yielded the desired Pauson-Khand products in good to moderate yields. A series of allylsilane derived enynes with varying substituents at both alkyne and alkene moieties were synthesised and subjected to Pauson-Khand reaction.

Silyl enol ethers as substrates for PKR

Pauson-Khand reactions of the TMS and TIPS enol ethers of model substrates, derived from diethyl malonate, were investigated. The methodology developed for these silyl enol ethers was then applied to the synthesis of a model substrate for ingenol.

Synthesis of model substrate for Ingenol

Ingenol, is a highly oxygenated tetracyclic diterpene, isolated initially from the *Euphorbia ingens* species of the *Euphorbiaceae* plant family, by the Hecker group in 1968. It has attracted considerable interest from both the chemical and biological communities because of its unique structure and an array of biological properties. Ingenol has a *trans*-intrabridgehead BC ring junction. We have investigated the possibility of using the PKR to synthesise the ring skeleton of ingenol in an atom efficient and stereospecific manner.

To my family

ACKNOWLEDGEMENTS

First and foremost I would like to thank Allah Almighty for his many blessings.

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I want to thank my family: especially my parents, for always believing in me, for their love, endless encouragement and support, my grandparents for their prayers, Irshad for being my personal IT consultant! and finally my mother and father in law for their support throughout my PhD and for babysitting Jumimah and Sulaiman (not an easy task!).

Finally, I want to express my love to Ilyas, whose encouragement and belief in me kept me going throughout this PhD. Thank you for your love, patience, support and for warming my feet!.

ABBREVIATIONS

acac	Acetylacetonyl
aq	Aqueous
Ar	Argon
atm	Atmosphere
Boc	*tert*-Butyloxycarbonyl
^{t}Bu	*tert*-Butyl
n-BuSMe	*n*-butyl methyl sulphide
C_6H_6	Benzene
CH_3CN	Acetonitrile
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
$CoBr_2$	Cobalt(II)bromide
CO	Carbon monoxide
CO_2	Carbon dioxide
cod	Cycloocta-1,5-diene
$Co_2(CO)_8$	Dicobalt octacarbonyl
$Co_4(CO)_{12}$	Tetracobalt dodecacarbonyl
Cp_2TiCl_2	Titanocene dichloride
$Cp_2Ti(PMe_3)_2$	Bis(trimethyphosphine)titanocene
Cp_2ZrCl_2	Zirconocene dichloride
CTAB	Cetyltrimethylammonium bromide
CTAHS	Cetytrimethylammonium hydrogen sulphate
CuCl	Cuprous chloride
$CyNH_2$	Cyclohexylamine
DCE	1,2-Dichloroethane
DMAc	*N,N*-dimethylacetamide
DMAP	Dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
DSAC	Dry state adsorption conditions

eq	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
Et_3SiH	Triethylsilane
h	Hours
HIV	Human Immunodeficiency Virus
H_2O_2	Hydrogen peroxide
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KHMDS	Potassium hexamethyldisilazide
L	Ligand
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamine
LHMDS	Lithium hexamethyldisilazide
LiCl	Lithium chloride
M	Molar
Me	Methyl
MeOH	Methanol
MS	Molecular sieves
N_2	Nitrogen
NaH	Sodium hydride
NaI	Sodium iodide
NMO	4-methylmorpholine-*N*- oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
O_2	Oxygen
PBr_3	Phosphorus tribromide
PBu_3	Tributyl phosphine
Ph	Phenyl
$PhCH_3$	Toluene
PKC	Protein Kinase C
PKR	Pauson-Khand reaction
^iPr	Isopropyl
rt	Room temperature

$[Rh(CO)_2Cl]_2$	Rhodium(I)dichloride dimer
Sat.	Saturated
SAR	Structure Activity Relationship
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Triflouromethanesulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
tlc	Thin layer chromatography
TMANO	Trimethylamine-*N*-oxide
TMS	Trimethylsilyl
$Ru_3(CO)_{12}$	Triruthenium Dodecacarbonyl
Ts	*para*-Toluenesulfonyl

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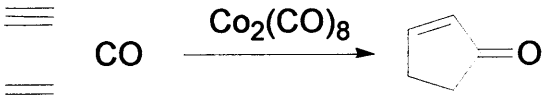
1 Introduction

1.1 The Pauson-Khand reaction

The synthesis of organic carbocyclic and heterocyclic systems from acyclic building blocks is usually achieved by either condensation or cycloaddition processes. Organic cycloaddition reactions allow the synthesis of a variety of systems especially ones containing 3- to 7-membered rings. These cycloaddition processes can involve reaction of two or more components. Transition metals have been known to induce a wide variety of organic reactions including cycloaddition reactions. As a fuller understanding of transition metal mediated reactions has evolved, the rational development of new and more selective transformations has begun to take place. This introduction chapter deals with cycloaddition of alkynes, alkenes and carbon monoxide to form cyclopentenones, the Pauson-Khand reaction. Several reviews of Pauson-Khand reaction have appeared in the literature.[1, 2, 3, 4, 5, 6, 7]

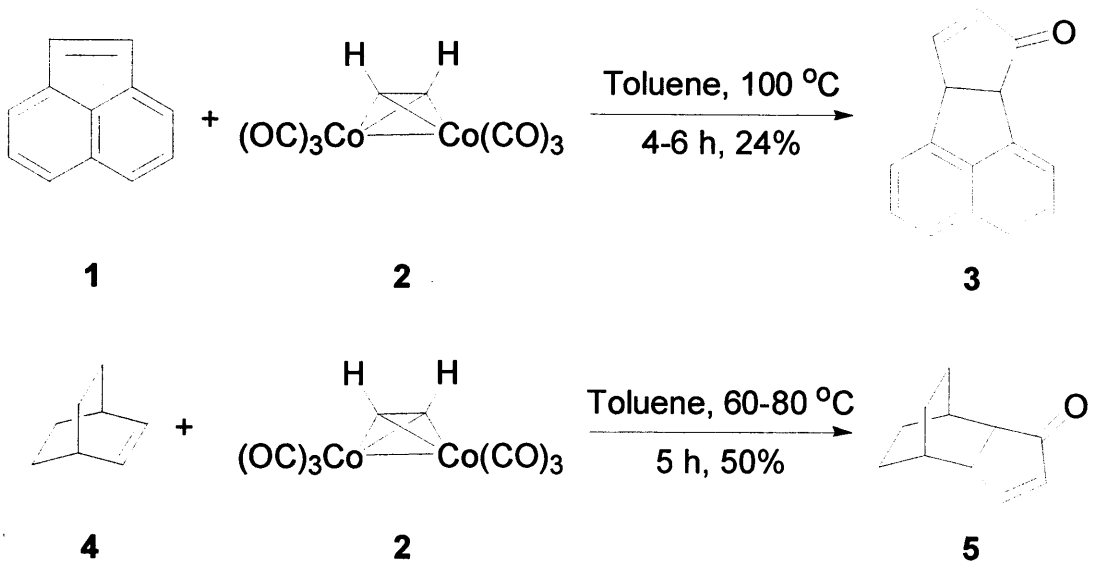
The Pauson-Khand reaction[8], a formal [2+2+1] cycloaddition of an alkene π bond, an alkyne π bond and carbon monoxide to form a five-membered ring, was discovered in the early 1970's and is summarised in **Scheme 1**.



Scheme 1

The reaction was discovered accidentally in a study aimed at the preparation and characterisation of alkyne complexes derived from dicobalt octacarbonyl, metal-free compounds containing a cyclopentenone were also isolated.

In the original procedure, the alkyne was allowed to react with a stoichiometric amount of dicobalt octacarbonyl at room temperature over several hours in hydrocarbon or ethereal solvent to generate a dicobalt hexacarbonyl complex of the alkyne, which then reacted with an alkene upon heating to generate a cyclopentenone[1].**Scheme 2** illustrates two of the earlier examples of intermolecular Pauson-Khand cyclisation.[9, 10]



Scheme 2

While this reaction represented a dramatic increase in molecular complexity from starting materials to product, the reaction was somewhat limited in its application to synthesis of complex molecules. For instance, unless strained alkenes were used, the efficiency of the cycloaddition was typically low and the use of unsymmetrical alkenes led to mixtures of cyclopentenone regioisomers. The reaction was also sensitive to steric and electronic effects of the substituents introduced into either the alkene or the alkyne precursors. Finally, the conditions required to effect the cycloaddition (high temperatures and long reaction times) led in many cases to decomposition of starting materials and/or products.[4]

Making the reaction intramolecular by attaching the alkene and alkyne through a carbon tether increased the synthetic utility of the reaction; strained olefins were also no longer required and the reaction became regioselective with respect to the olefin.[11]

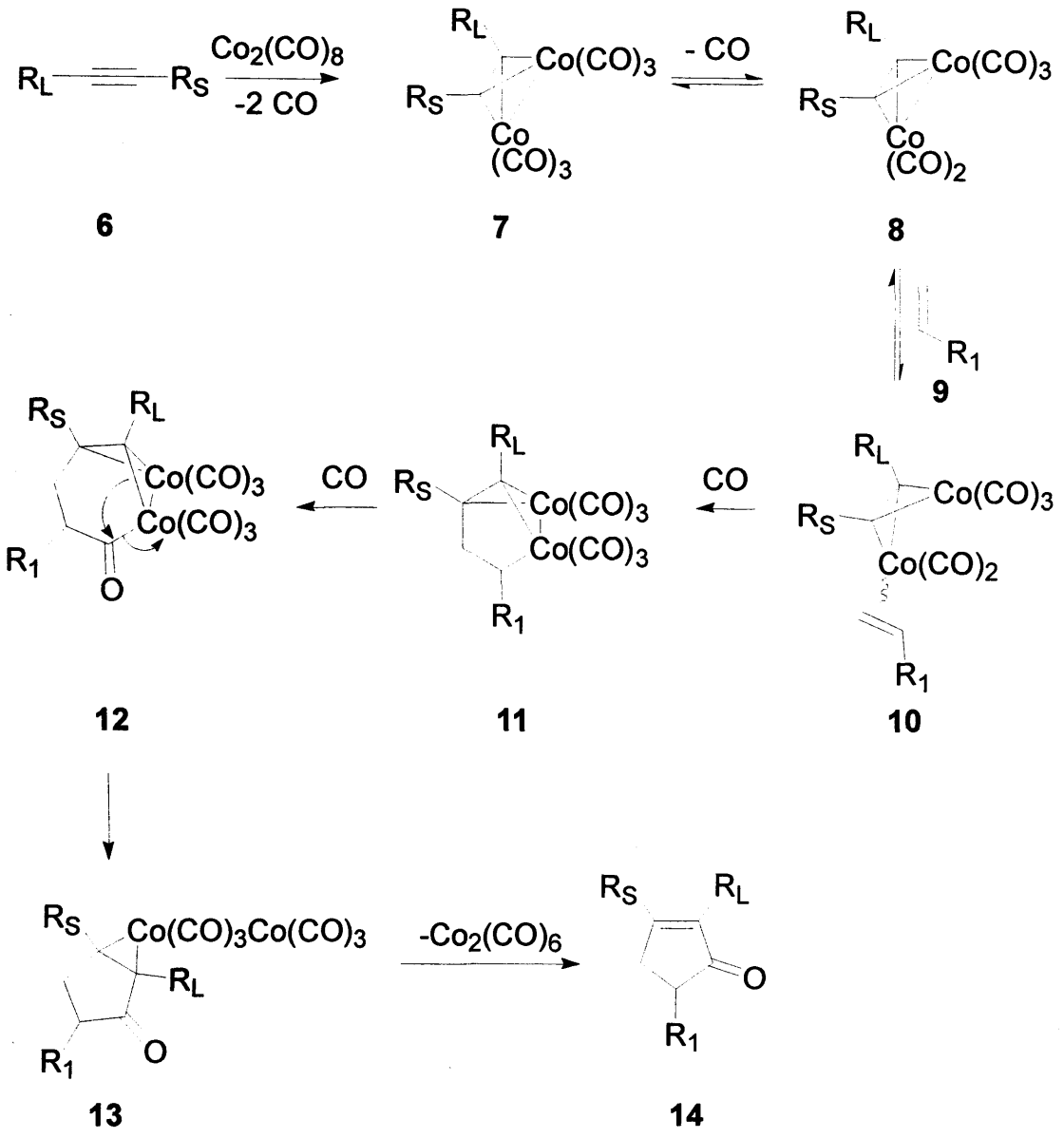
Major methodological improvements appeared in late 1980s and in the early 1990s, which increased the scope of the reaction further. These included adsorption of the enyne onto a chromatographic support, and addition of one of a number of 'promoters'. More recently, catalytic and stereoselective version of the Pauson-Khand reaction have been developed, as have similar reactions employing metals other than cobalt. These

advances in the Pauson-Khand reaction methodology as well as mechanism of this reaction will be reviewed in the following sections.

1.2 Mechanism of the Pauson-Khand reaction

Beyond the fact that a dicobalt hexacarbonyl alkyne complex is involved, little is actually known about the mechanism of the Pauson-Khand cycloaddition. Magnus originally proposed the currently accepted mechanistic pathway in 1985[12]. Direct studies on the mechanism have been limited by the fact that attempts to observe intermediates of the reaction pathway beyond the alkyne complexation stage have been unsuccessful, final products being the only detectable species during the course of the reaction.[1]

It is generally assumed that the rate-limiting step occurs early in the sequence preventing the build up of any subsequent intermediates to observable levels. The current understanding of the mechanism of the Pauson-Khand reaction has been inferred from the regio- and stereochemistry observed in the products. These observations include characterisation of isolable alkyne dicobalt hexacarbonyl complexes, an isolable pentacarbonyl complex stabilised by chelation of a bishomopropargylic-sulfide group[13] and an intercepted intermediate[14].
The mechanism is illustrated schematically in **Scheme 3**.



Scheme 3

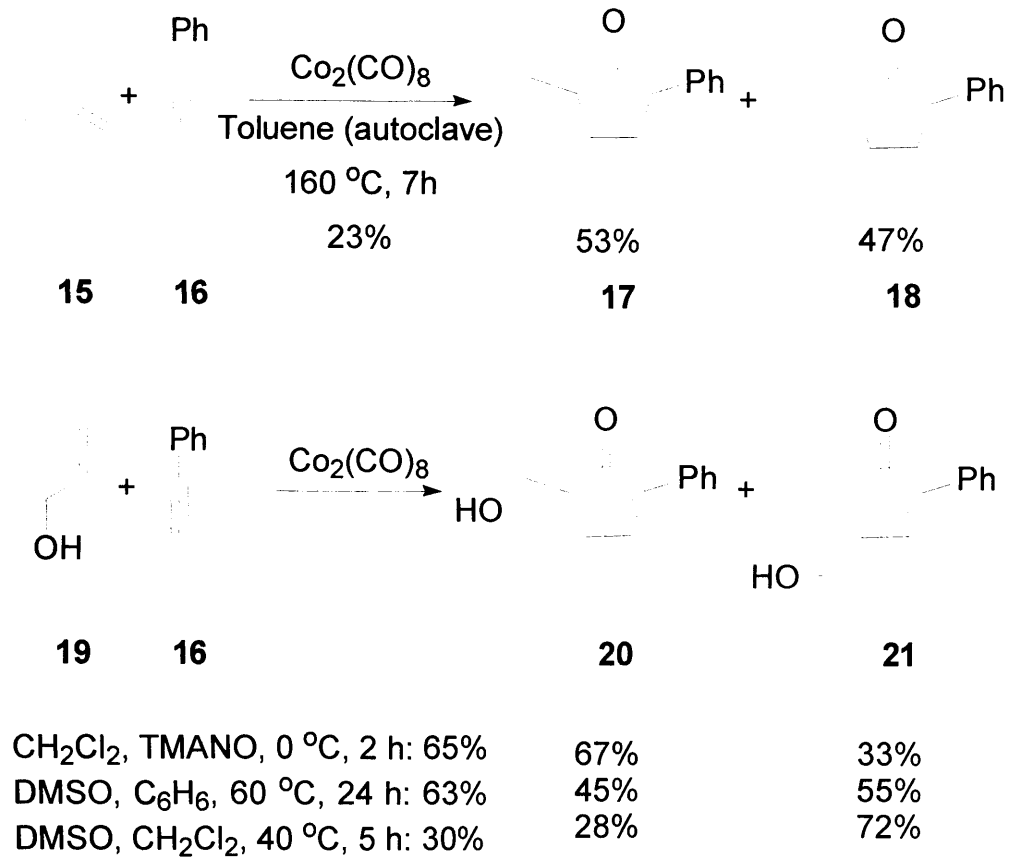
The initial step involves complexation of the alkyne triple bond with dicobalt octacarbonyl to form dicobalt hexacarbonyl complex **7**. The reaction involves five main steps from this initial complex **7**: (i) decarbonylation of **7**, (ii) coordination of an olefin onto a coordinatively unsaturated cobalt centre in **8**, (iii) insertion of the π-complexed olefin into a Co-C bond (**11**), (iv) insertion of CO into a Co-C sp^3 bond (**12**), and (v) reductive elimination and subsequent loss of a dicobalt carbonyl fragment to give the final cyclopentenone **14**.

1.2.1 Regiochemistry of cycloaddition

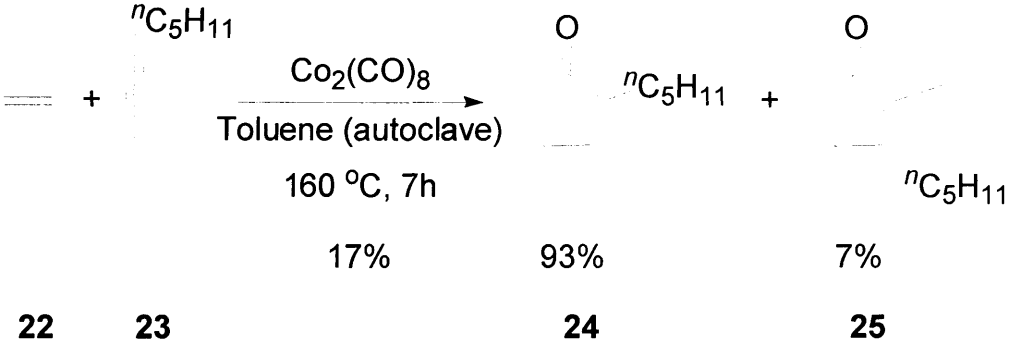
The principal interactions that control the regio and stereochemistry of the Pauson-Khand reactions appear to be steric in nature. It is usually assumed that complexation of the alkene to one cobalt atom takes place via a dissociative mechanism involving loss of CO. This process is thought to be reversible. In the amine-*N*-oxide promoted reaction, CO_2 is liberated in the first step and the first step becomes irreversible. Subsequently irreversible insertion of the complexed face of the alkene π-bond into one of the formal cobalt-carbon bonds of the alkyne complex occurs. This step is probably both rate and product determining and is followed by addition of CO to the coordinatively unsaturated cobalt atom. The metallocycle that forms may proceed to product by a standard sequence of steps beginning with migratory insertion of a cobalt bound CO, addition of a ligand and reductive elimination of the $Co(CO)_3$ moiety. The $Co_2(CO)_6$ fragment of the final enone leads to the product via the loss of $Co_2(CO)_6$ fragment.[1]

Regiochemistry with respect to both alkyne and alkene is determined during the insertion in the cobalt carbon bond[1]. The incipient carbon-carbon bond is most susceptible to steric crowding. If the alkyne is unsymmetrical, insertion and carbon-carbon bond formation proceed exclusively at the alkyne carbon possessing the smaller substituent.

Alkene regiochemistry in the Pauson-Khand reaction is less readily predicted, as it is dependent on the nature of both the alkene and the alkyne. Upon reaction with ethyne or terminal alkynes, terminal alkenes typically display minimum regioselectivity, which may vary with reaction conditions, although the incorporation of alkyne remains totally regioselective as shown in **Scheme 4**. Alkyne regiocontrol stays high in the reactions with ethene, even though steric interactions are rather small (**Scheme 5**).



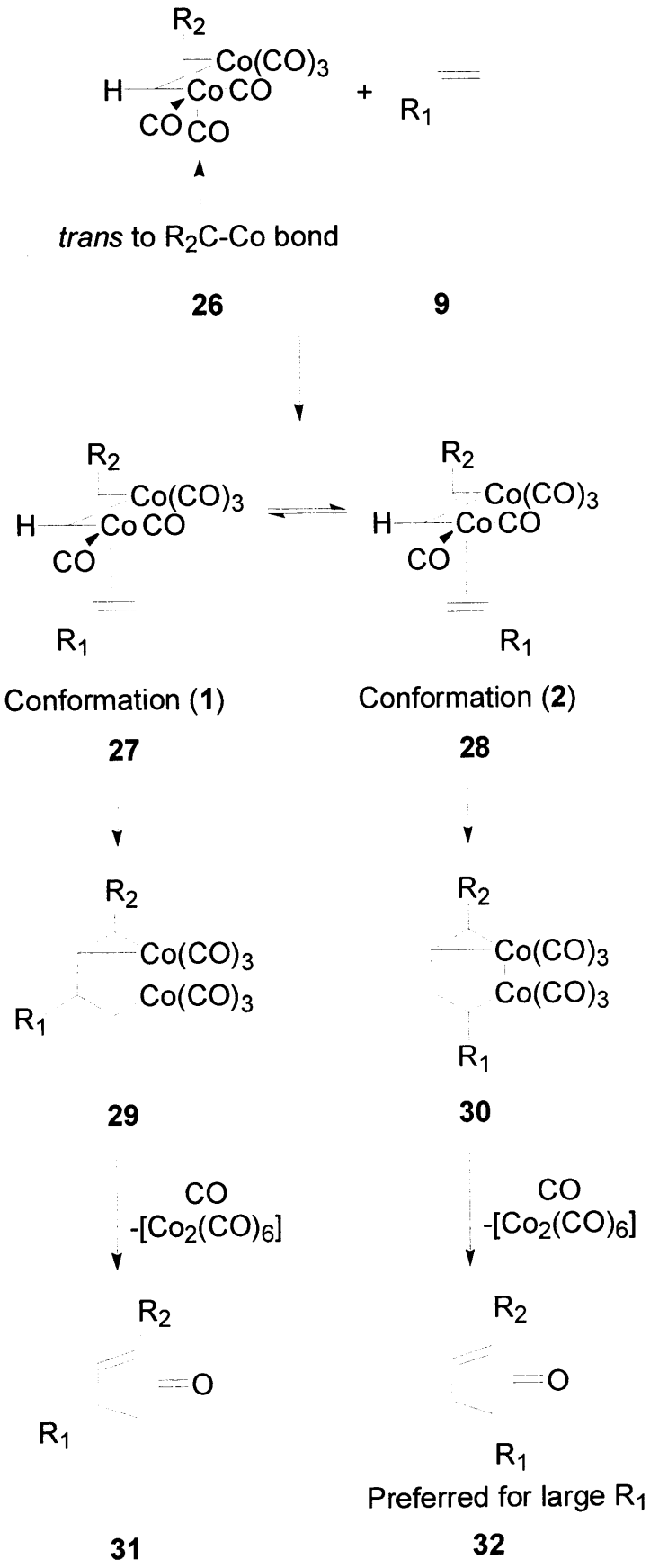
Scheme 4



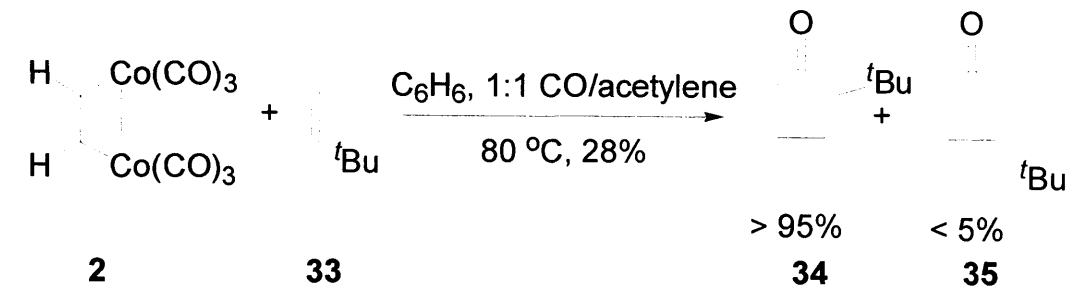
Scheme 5

Reactions of monosubstituted alkenes with internal alkynes lead to the 2,3,5-trisubstituted isomer as the major product. It is assumed that the isomer of pseudooctahedral cobalt (**26**), that leads to insertion of alkene contains the alkene complexed *trans* to the bond between the cobalt and the substituted alkyne carbon, avoiding a steric interaction with the latter (**Scheme 6**)[1]. Insertion can therefore only occur into other cobalt-carbon bond, fixing the alkyne regiochemistry.

With most terminal alkynes, there is little preference between the two possible conformations about the cobalt-alkene bond, resulting in no regioselectivity in the alkene insertion. However if the R_1 group on alkenes is sufficiently large, conformation (**2**) is preferred as shown in **Scheme 6**, placing the large group onto the cobalt–carbon bond away from R_2 of the alkyne. This results in a preference for the 5-substituted cyclopentenone (**32**) as shown in **Scheme 6**. Pauson-Khand reaction illustrated in **Scheme 7** demostrates this point. Reaction of alkene **33** with dicobalt hexacarbonyl complex of acetylene led to 5-substituted cyclopentenone **34** as major product.

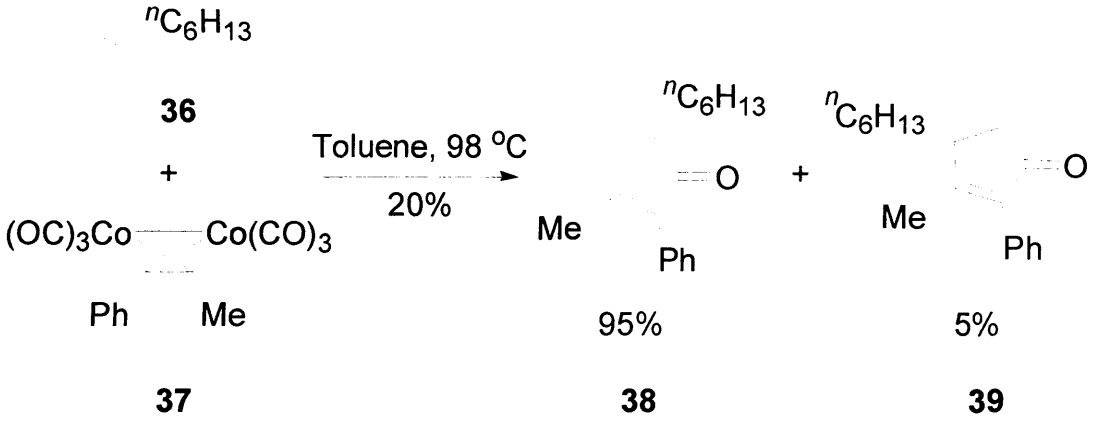

R2
Co(CO)3
H
Co CO
CO CO
+
R1
trans to R2C-Co bond
26
9
R2
Co(CO)3
H
Co CO
CO
R1
Conformation (1)
27
R2
Co(CO)3
H
Co CO
CO
R1
Conformation (2)
28
R2
Co(CO)3
Co(CO)3
R1
29
R2
Co(CO)3
Co(CO)3
R1
30
CO
-[Co2(CO)6]
CO
-[Co2(CO)6]
R2
O
R1
31
R2
O
R1
Preferred for large R1
32

Scheme 6



Scheme 7

Krafft has provided support for this picture by observation of greatly increased alkene regioselectivity in Pauson-Khand cycloaddition with internal alkynes as shown in **Scheme 8**. 2,3,5-Substituted cyclopentenone **38** was the major product in this reaction[15].

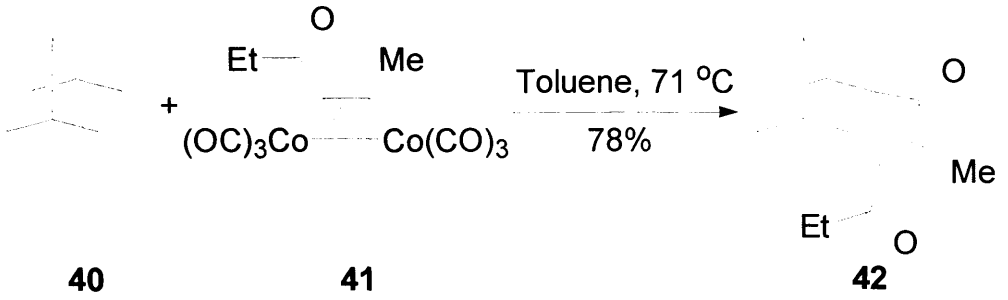


Scheme 8

The site of co-ordination of the alkene determines alkyne regioselectivity, while the conformation of the coordinated alkene prior to insertion contributes to alkene regioselectivity. The presence of groups larger than hydrogen on both alkyne carbons introduces unavoidable steric interactions that lead to preference for conformation (2) in **Scheme 6**.

Initial support for the proposed mechanism cited steric control of the regiochemical outcome of the intermolecular reactions. However electronics have also been shown to have an effect on the regiochemical product mixture.

Cycloadditions of conjugated alkynones and alkynoate esters proceed exclusively to give cyclopentenones in which the ketone or ester function is located at C-3 (**Scheme 9**)[16]. While this result is consistent with steric origin (*i.e.* tetrahedral carbon being larger than trigonal carbonyl carbon), the complete regioselectivity is surprising considering the rather small size differential involved. It is suggested that an electronic component is involved and that bond formation between the more electron rich α-carbon of the triple bond and an alkene carbon is favoured.

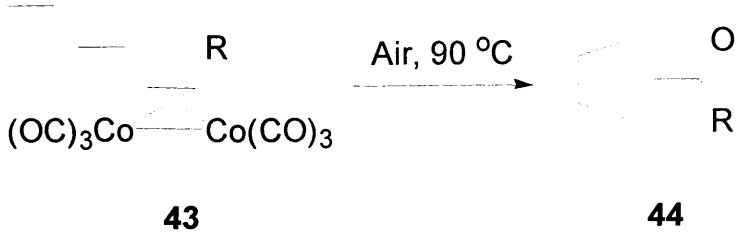


Scheme 9

1.2.2 Evidence in support of the proposed mechanism

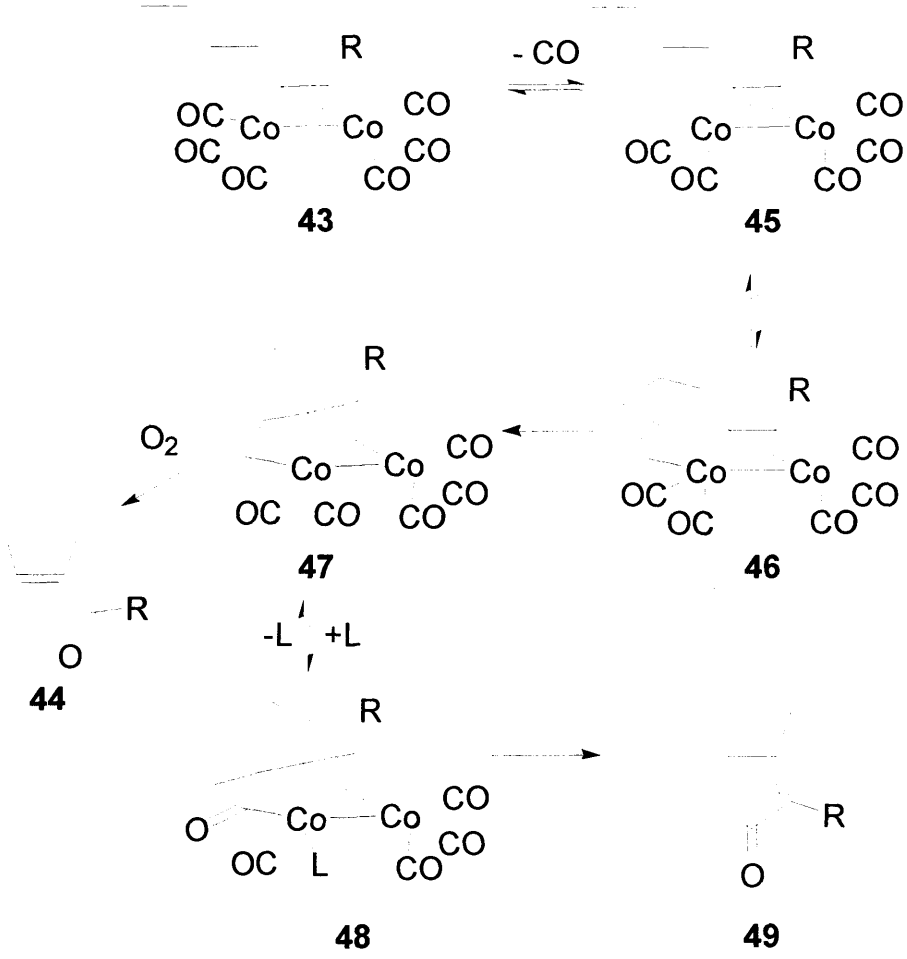
1.2.2.1 Interrupted PKR

Krafft has successfully interrupted the intramolecular cycloaddition process by exposing the reaction mixture to an oxygen-containing atmosphere as shown in **Scheme 10**. Monocyclic products of type **44** were isolated, in which oxygen had been incorporated instead of carbon monoxide insertion and the cyclisation to form the second ring had not proceeded in the normal fashion[14].



Scheme 10

Although, the actual role of molecular oxygen in interrupting the normal Pauson-Khand reaction is unclear, Krafft has suggested that both the enone product **44** and the expected cyclopentenone product **49** can arise from a common intermediate **47** in the proposed mechanism as shown in **Scheme 11**. The interception of **47** by molecular oxygen, perhaps at the metal centre, could inhibit carbon monoxide insertion, and therefore be responsible for driving the reaction towards the observed enone **44**.[14]



Scheme 11

1.2.2.2 Isolation of a pentacarbonyl intermediate

Krafft has found that the rate of cycloaddition of 1,6-enynes is accelerated by the presence of sulfur, nitrogen or oxygen in the homopropargylic or bishomopropargylic position[13]. Upon heating, the heteroatom-substituted substrates, especially sulfur substituted substrates, reacted faster than their corresponding analogues, without the coordinating heteroatoms. During the course of their studies of 4-methylmorpholine-*N*-

oxide promoted reactions with complexes of sulfur-substituted substrates, they isolated a new intermediate **50** which represents a trapped form of pentacarbonyl intermediate in the proposed mechanism for the Pauson-Khand reaction (**Figure 1**). They also isolated a similar, more stable intermediate **51**. The NMR spectra of both **50** and **51** showed absence of alkene coordination and indicated the presence of coordinated sulfur (shift of the protons adjacent to sulfur and a nonequivalence of the methylene protons on the tether between the alkyne and the sulfide).

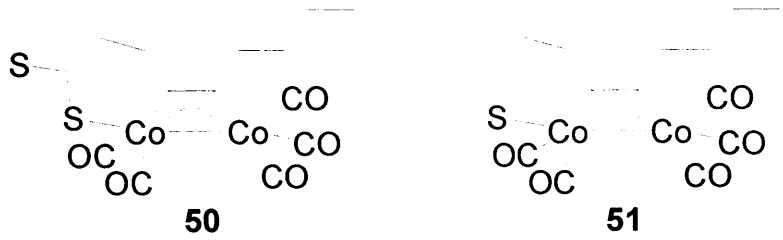
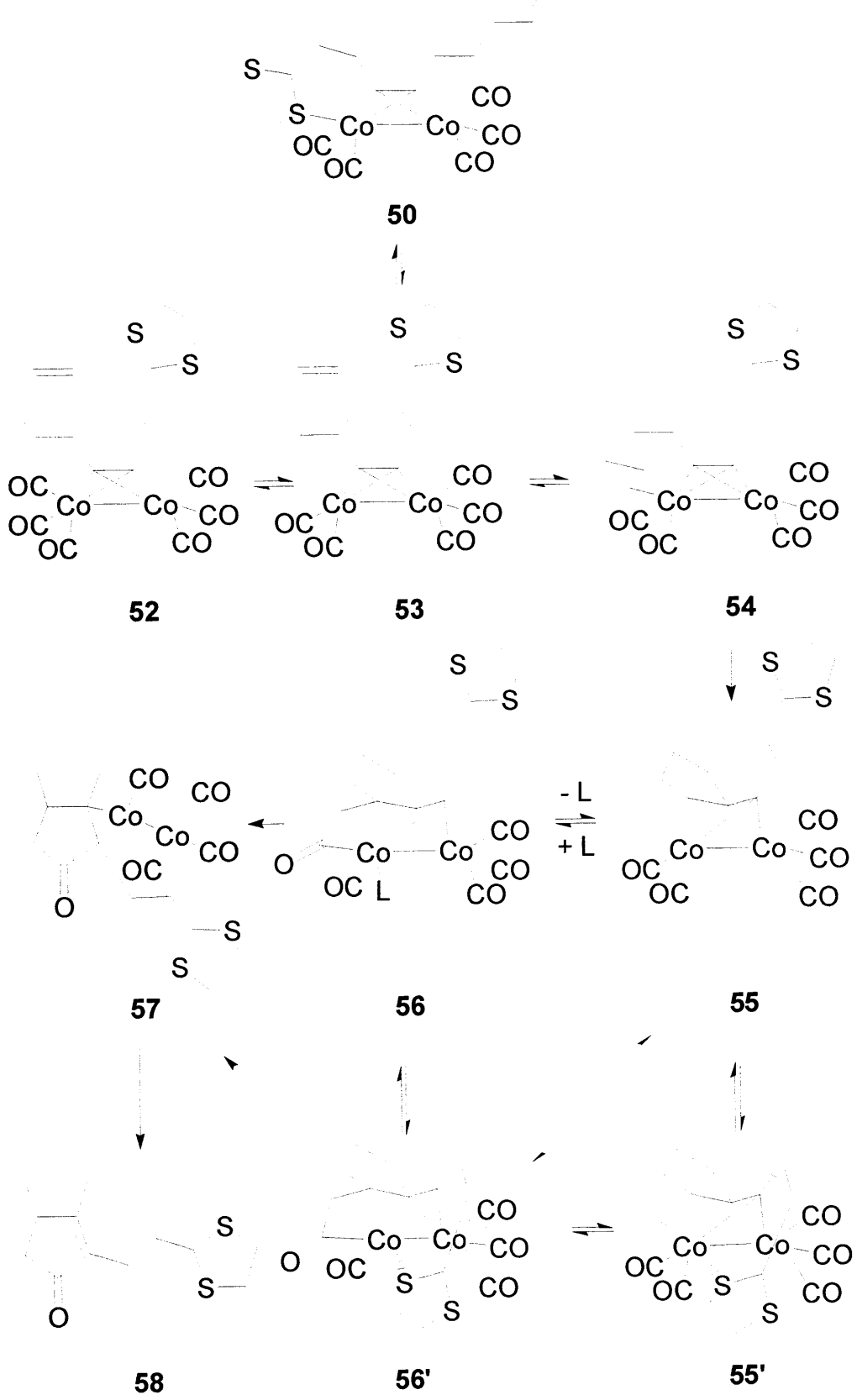


Figure 1

Krafft has rationalised these results within the context of the proposed mechanistic pathway. Their rationale is illustrated in **Scheme 12**.



Scheme 12

Three steps in the proposed mechanism, **52** to **53**, **54** to **55**, and **55** to **56**, necessarily generate a vacant coordination site. Judicious placement of a coordinating ligand can be expected to lead to a stabilisation of coordinatively unsaturated complex by heteroatom complexation to the metal centre. Stabilisation of the pentacarbonyl complex **53** by formation of a coordinatively saturated complex **50** may be considered as rate decelerating with increasing stability of **50**. Transformations **54** to **55** and **55** to **56** may be driven by heteroatom coordination to provide complexes **55'** or **56'**, respectively. This acceleration may be a result of insertion of CO in complex **55'** occurring faster than in **55** as a result of heteroatom coordination. Alternatively, decarbonylation of **56** may be inhibited due to coordination of the heteroatom in **56'**. The bishomopropargylic ligand would be expected to provide a more stable complex (six-membered chelate ring) than the homopropargylic cases (five-membered chelate ring) due to the strain in a five membered chelate ring caused by the bond angle at the carbon bound to cobalt. Interaction of the coordinating ligand in **55** or **56** could be viewed as a rate-accelerating role which can compensate for the decrease in rate caused by the formation of complex **50**. Krafft postulates that these findings and new intermediates, isolated during the course of the reaction, support the dissociative loss of CO from the initial dicobalt hexacarbonyl complex to form dicobalt pentacarbonyl complex which in turn leads to complexation and insertion of alkene. Pericas and coworkers have also isolated similar sulfur chelated dicobalt pentacarbonyl intermediates which support this dissociative loss of CO from dicobalt hexacarbonyl complex[17, 18, 19].

1.2.2.3 Theoretical studies

Several theoretical studies support this generally accepted mechanism. Pericas has studied both the initial complexation and then the insertion of alkene into pentacarbonyl dicobalt intermediate using density functional studies[20]. The author has shown the importance of facilitaing CO dissociation from the dicobalt hexacarbonyl complex but points out that this is not a sufficient condition for the reaction and the energy of olefin complexation and insertion is also very important. This is the reason why strained olefins react so well as in this step strain of the cyclic olefins is liberated, favouring the process[17, 18, 19].

Other authors including Nakamura[21] and Milet and Gimbert[22] have performed high level theoretical calculations on the cobaltacycle formation step. These studies suggest that

the insertion of the olefin is the critical stereo- and regiochemical determining step of the Pauson-Khand reaction. Nakamura points out that while the bond forming events occur on one metal atom, the other metal atom acts as an anchor and also exerts electronic influences on the other through the metal-metal bond.

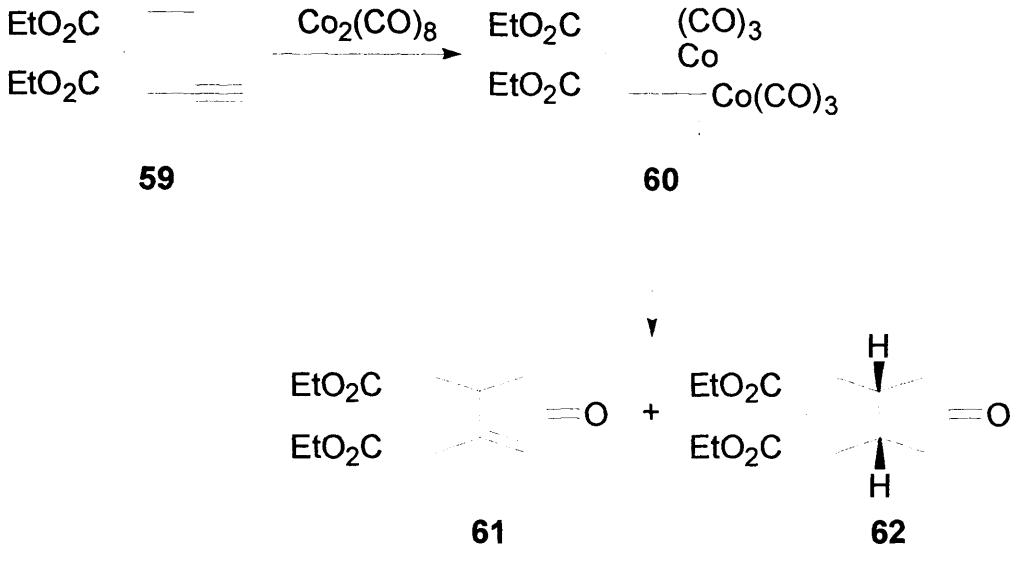
Further study is required to firmly establish the mechanism aspects of the Pauson-Khand reaction. This is especially true with the development of reaction variations including the use of alternative metals and catalytic processes.

1.3 Stoichiometric Pauson-Khand reaction

The main drawbacks of the Pauson-Khand reaction as originally described were its relatively narrow scope and, in many cases, poor conversions. Over the past few years there has been a remarkable increase in the scope and applicability of the reaction due to the development of new reaction conditions such as the use of 'promoters' or 'additives' to accelerate and/or increase the yields of reactions. Several metals other than cobalt have also been employed in carrying out stoichiometric Pauson-Khand reactions. This section discusses these methods.

1.3.1 Polar Solvents

Polar solvents such as acetonitrile (CH_3CN), dimethyl sulfoxide (DMSO) and methanol (MeOH) have been shown by Pauson and coworkers to promote both inter- and intramolecular Pauson-Khand reaction[23]. The effect of DMSO and other polar solvents on intramolecular Pauson-Khand cyclisation of allyl propargyl malonate was studied by Pauson and co-workers and some of the results are shown in **Scheme 13** and **Table 1**.



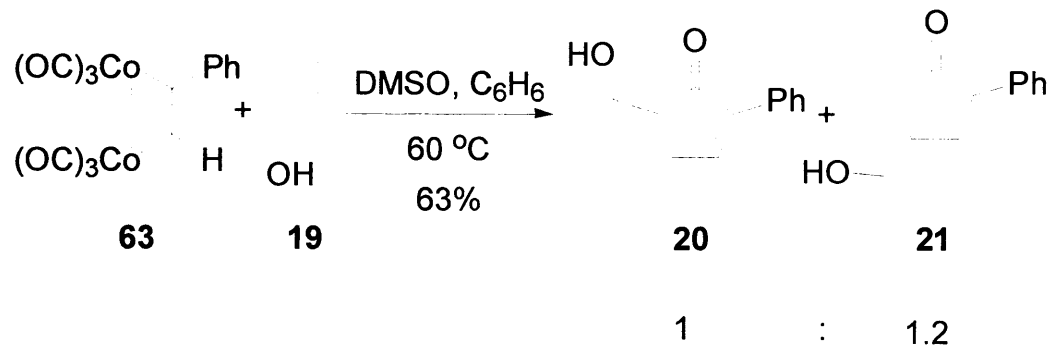
Scheme 13

Table 1. Effect of DMSO on PKR of 59

Entry	Promoter	Solvent	T (°C)	Time (h)	Yield %	
					61	**62**
1	None	CH_2Cl_2	40	36	25	2
2	DMSO (1eq)	CH_2Cl_2	40	4	85	1
3	DMSO (3 eq)	CH_2Cl_2	40	4	83	0
4	DMSO (3 eq)	C_6H_6	40	24	92	0

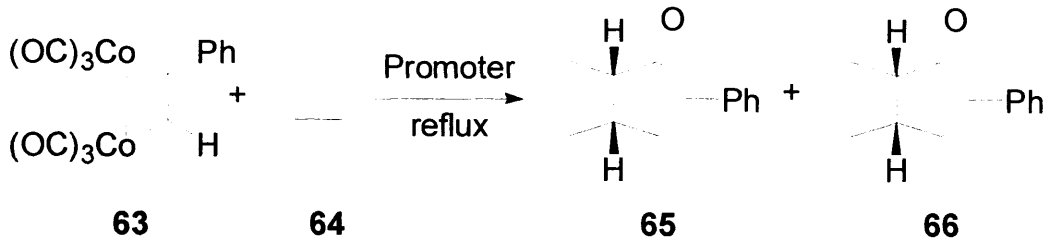
In the absence of DMSO (entry 1), yield of both **61** and **62** was poor whereas in the presence of 1 or 3 equivalents of DMSO (entries 2 & 3) yield of **61** improves dramatically. Formation of the saturated ketone byproduct **62** is avoided by replacing dichloromethane (CH_2Cl_2) as solvent with benzene (C_6H_6) (entry 4). The latter also gives better yields, albeit with longer reaction times.

DMSO has also been shown to promote intermolecular Pauson-Khand reaction. Results show successful use of unprotected allyl alcohol **19** in the DMSO promoted reaction as shown in **Scheme 14**. Protection of alcohol had previously been found to be necessary under higher temperature conditions[24].



Scheme 14

The effect of a series of polar solvents including CH_2Cl_2, MeOH, CH_3CN, THF and Et_2O was studied on the Pauson-Khand reaction depicted in **Scheme 15**. All were shown to have a promoting effect on the Pauson-Khand reaction (**Table 2**). Both CH_3CN (entry 2) and MeOH (entry 6), while requiring slightly longer reaction times gave comparable and slightly better yields. These conclusions relate primarily to CH_2Cl_2 solutions of the promoters; when in place of this, chloroform ($CHCl_3$) was used as the solvent, the reaction yielded variable but substantial amounts of the corresponding saturated ketone byproduct **66** (entries 3 & 7).



63 **64** **65** **66**

Scheme 15

Table 2. Effect of polar solvents on PKR of 63 & 64

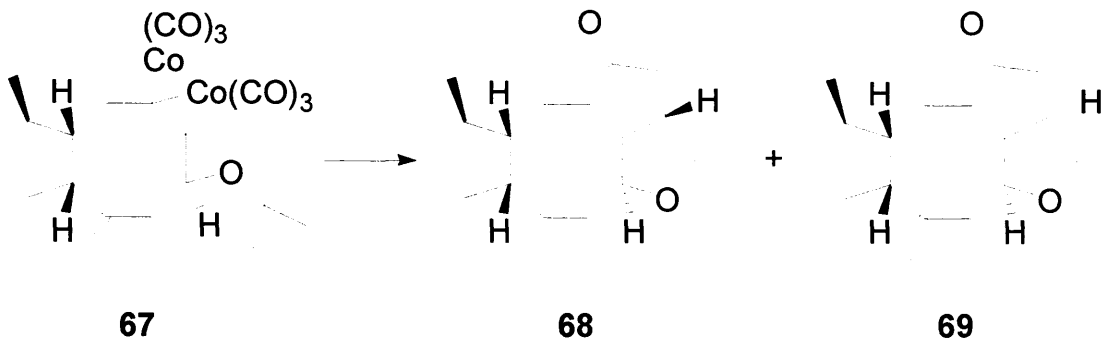
Entry	Promoter	Solvent	Time	Yield (%) **65**	Yield (%) **66**
1	DMSO	CH_2Cl_2	9h	71	-
2	CH_3CN	CH_2Cl_2	48h	70	-
3	CH_3CN	$CHCl_3$	16h	67	22
4	CH_3CN	CH_3CN	16h	51	-
5	CH_3CN	THF	24h	53	-
6	MeOH	CH_2Cl_2	3d	75	-
7	MeOH	$CHCl_3$	40h	29	36
8	MeOH	Et_2O	64h	68	5

1.3.2 Amine-N-Oxides

In the early 1990s, Schreiber[25] and Jeong[26] independently reported the promotion of Pauson-Khand reaction at room temperature using 4-methylmorpholine-*N*-oxide (NMO) and trimethylamine-*N*-oxide (TMANO) respectively.

A typical reaction protocol by Schreiber involves treating the cobalt complex of an enyne with six molar equivalents of NMO at room temperature followed by stirring at room temperature until completion of the reaction[25]. The mild reaction conditions allow for the incorporation of various functional groups in the cyclization process; alcohols, ethers, silyl ethers, acetals and remote olefins remain intact during the reaction. The lower temperature of the reaction also leads to higher levels of stereoselectivity as compared to corresponding thermal conditions. For example, cyclisation of dicobalt

hexacarbonyl complex **67** occurs to give a 4 : 1 ratio of **68** and **69** under thermal conditions whereas use of NMO increased the ratio to 11 : 1. (**Scheme 16, Table 3**)[25].



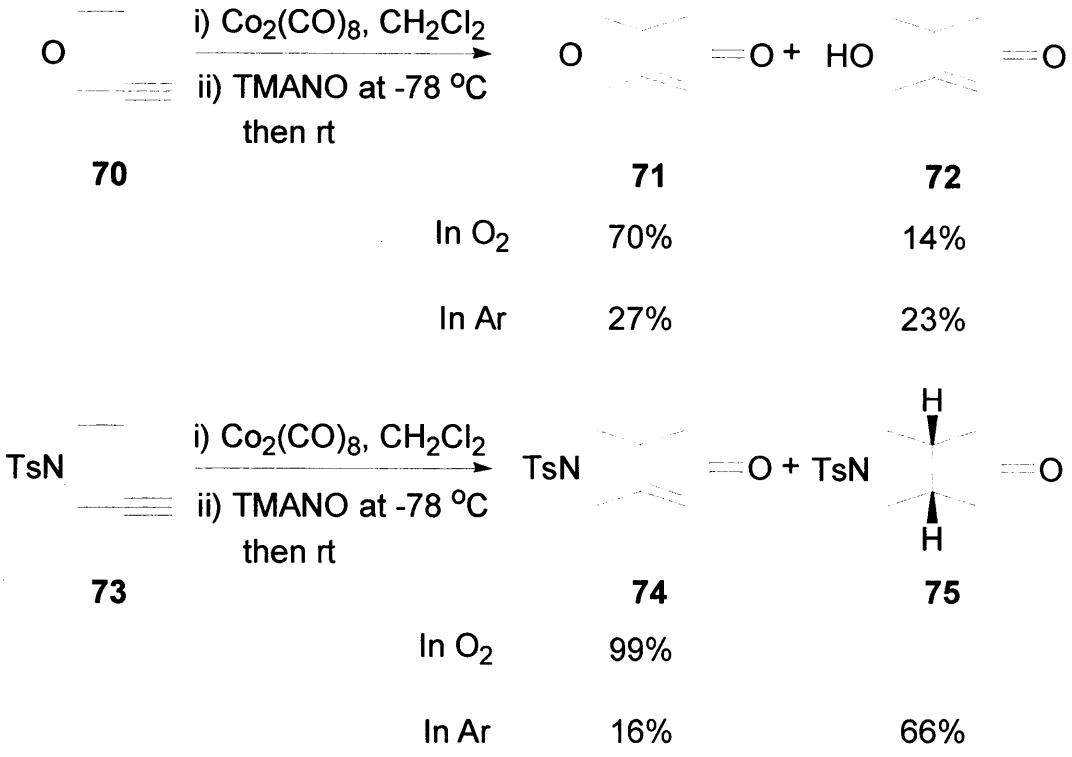
67 **68** **69**

Scheme 16

Table 3. Comparison of NMO & CH_3CN as promoters of PKR of 67

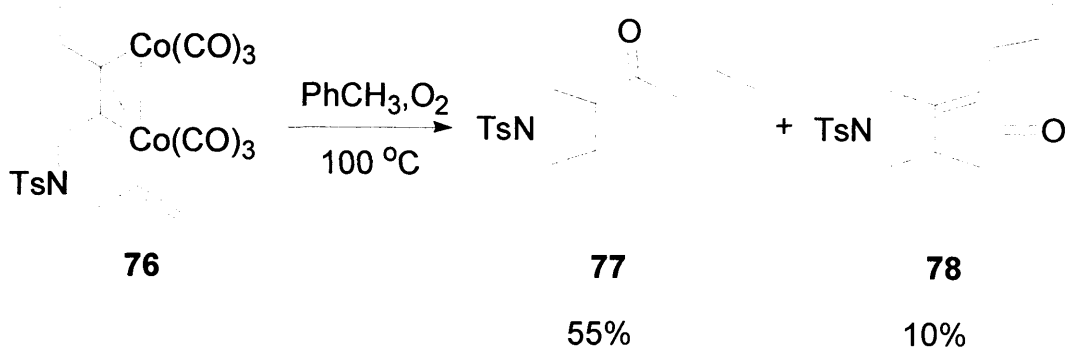
Entry	Conditions	Yield (%)	Selectivity (**68** : **69**)
1	NMO, CH_2Cl_2, rt	68	11 : 1
2	CH_3CN, 82 °C	75	4 : 1
3	CH_3CN, 45 °C	45	3 : 1

Jeong has reported that for oxygen and nitrogen containing substrates (**70** & **73** respectively) the presence of O_2 during the reaction is quite crucial. In the absence of O_2 ring opened products are formed from oxygen containing substrates (**72**) and saturated ketones from the nitrogen containing substrates (**75**) along with the desired products as shown in **Scheme 17**.[26]



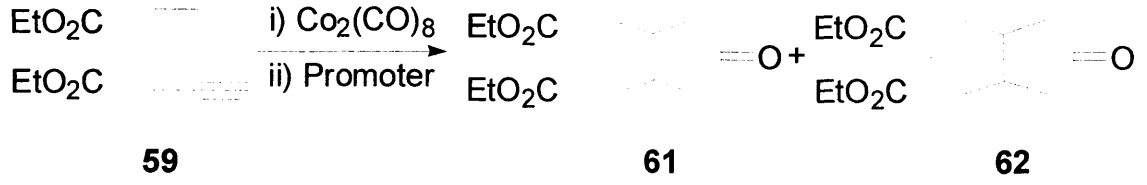
Scheme 17

These results are quite contradictory to the "interrupted Pauson-Khand reaction" reported by Krafft[14]. Thermal Pauson-Khand reaction of a range of cobalt complexed enynes in the presence of a controlled amount of oxygen led to monocyclic enones being isolated in addition to small quantities of expected Pauson-Khand enones. An example is illustrated in **Scheme 18**. The actual role of molecular oxygen in interrupting the normal Pauson-Khand reaction is unclear, however it is postulated that both the normal and interrupted Pauson-Khand products arise via a common metallacyclic intermediate (section 1.2.2.1, **Scheme 11**, p. 20).[14]



Scheme 18

Comparison of DMSO and TMANO as promoters of Pauson-Khand reaction showed that yields for the reaction illustrated in **Scheme 19** are similar although DMSO requires longer reaction times (**Table 4**, entry 3).



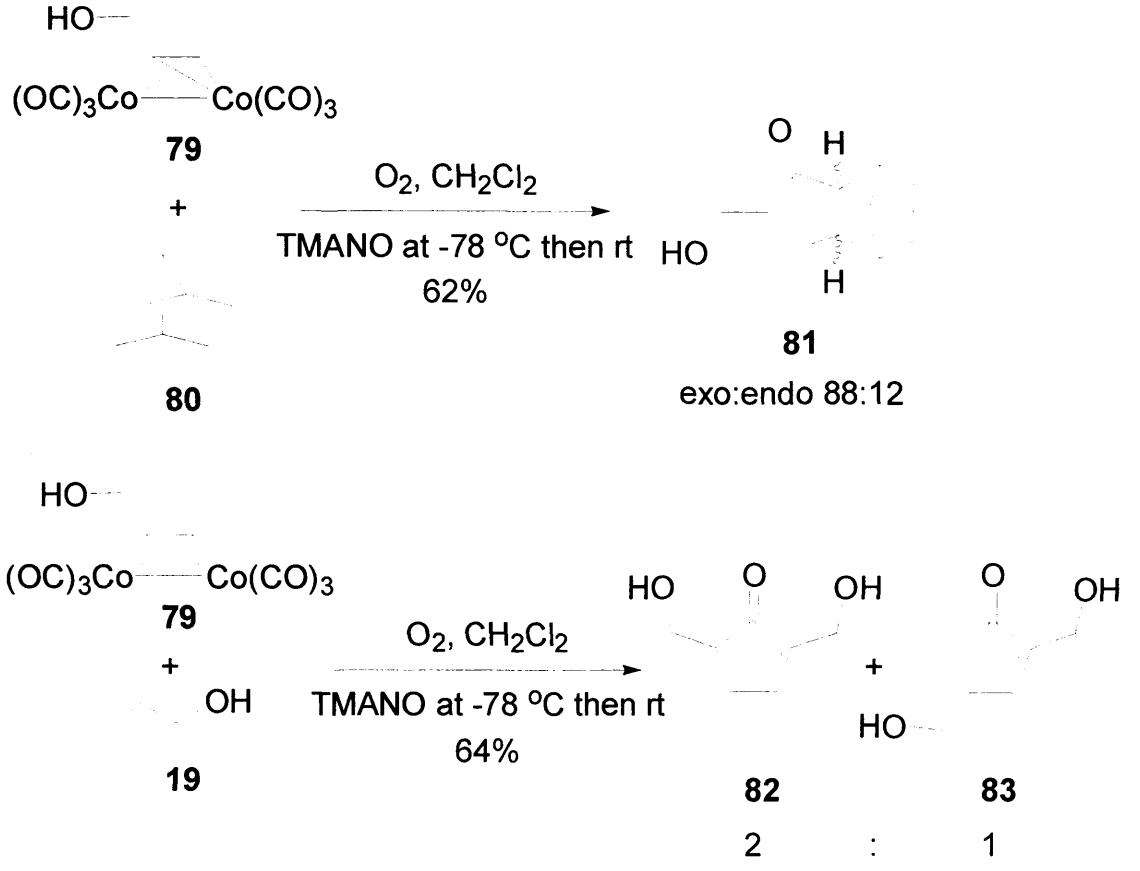
Scheme 19

Table 4. Comparison of DMSO and TMANO as promoters of PKR of 59

Entry	Promoter	Solvent	T (°C)	Time (h)	Yield % 61	62
1	TMANO	CH_2Cl_2	20	3	90	0
2	None	CH_2Cl_2	40	36	25	2
3	DMSO (3eq)	C_6H_6	40	24	92	0

The TMANO method has also been shown to make possible the use of both allylic and propargylic alcohol components without OH protection (which had previously been found to be necessary under higher temperature conditions.[24] **Scheme 20** illustrates two of the examples where both unprotected propargylic and allylic alcohol have been used[26]. Dicobalt hexacarbonyl of propargyl alcohol **79** reacts with norbornadiene **80** to

give the cycloadduct **81** in 62% yield. Dicobalt hexacarbonyl of propargyl alcohol **79** and allylic alcohol **19** react to give the cyclopentenones **82** and **83** in 64% yield.



Scheme 20

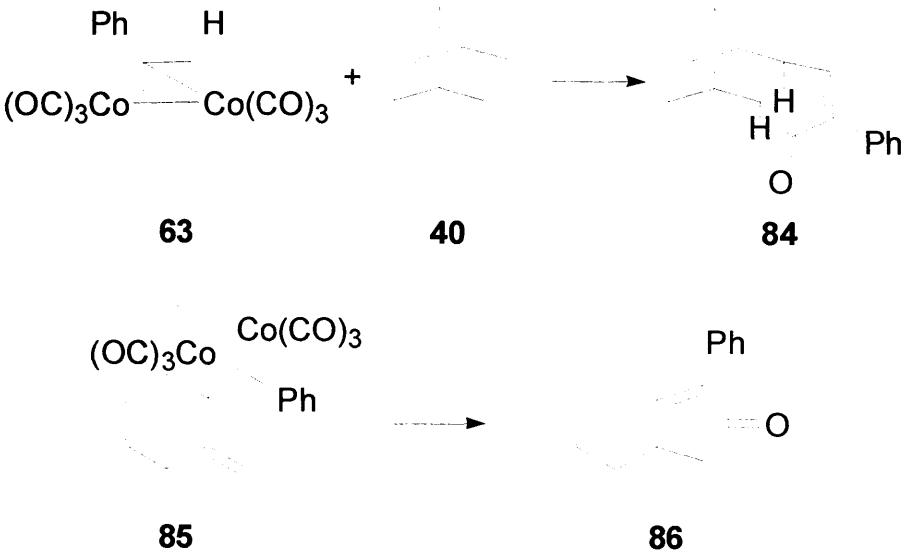
It seemed that the primary reason for requiring harsh reaction conditions (high temperature and pressure) for thermal Pauson-Khand reaction in its early stages was associated with the initial step of decarbonylation of dicobalt hexacarbonyl complex of the alkyne to generate a vacancy for the incoming alkene[25]. It has been known that amine-*N*-oxides such as trimethylamine-*N*-oxide (TMANO) and 4-methylmorpholine-*N*-oxide (NMO) can help make the ligand more labile on the transition metal complex of the alkyne[27] and in this case lead to oxidative removal of a carbon monoxide ligand, as carbon dioxide, from the cobalt and therefore create a vacancy for oxidative addition of alkene.

1.3.3 Primary Amines and Ammonia

Sugihara has reported the use of primary amines and ammonia in the rate enhancement of the Pauson-Khand reaction.[28] According to this study, primary amines with moderately hindered secondary alkyl groups such as cyclohexylamine ($CyNH_2$) dramatically increase the rate of Pauson-Khand cycloaddition. In addition, use of aqueous ammonium hydroxide in a biphasic system was reported.

As can be seen from **Table 5**, both methods gave comparable results in terms of yields and rates for both inter- and intramolecular Pauson-Khand reaction (**Scheme 21**). In all the cases they studied, the reaction was complete in a short time (10-135 min) and afforded the desired cyclopentenones in moderate to good yields (45-100%).

Sugihara postulates that amines act as hard ligands which react with the dicobalt hexacarbonyl complex of alkyne and facilitate the substitution of a CO ligand by the olefin. This labilising effect may also make the coordinated alkyne more reactive and therefore promote the reaction.



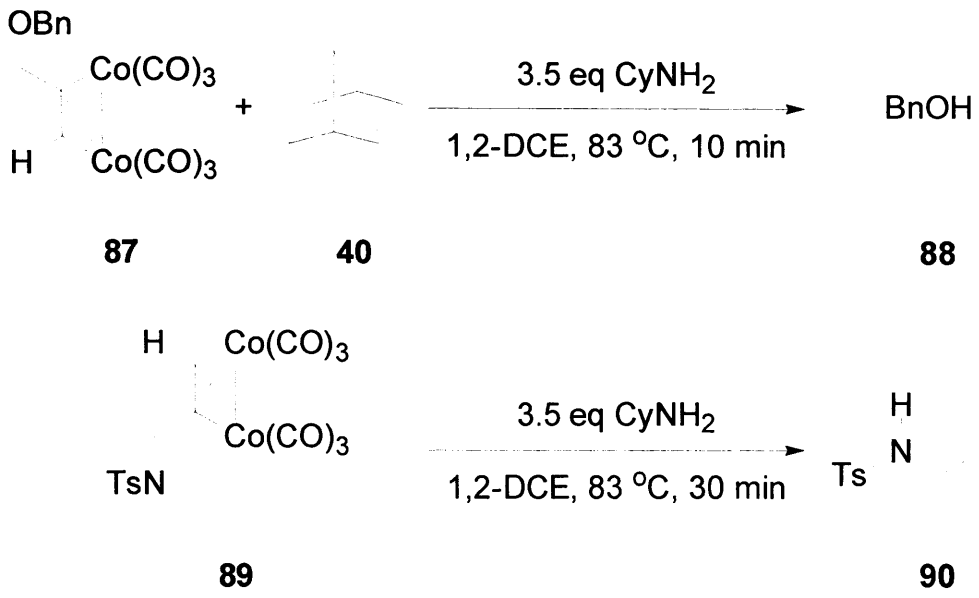
Scheme 21

Table 5. Cyclohexylamine and ammonia as promoters of PKR

Entry	Starting material	Product	Condition A		Condition B	
			t (min)	Yield (%)	t (min)	Yield (%)
1	**63** + **40**	**84**	10	98	10	100
2	**85**	**86**	30	90	30	90

Condition A: 3.5 eq of $CyNH_2$ in 1,2-dichloroethane at 83 °C. Condition B: 1:3 mixture (v/v) of 1,4-dioxane and 2M aq. NH_4OH at 100 °C.

The drawback of using this method is the formation of highly reducible cobalt complexes during the reaction which in some cases, induce the cleavage of a carbon-heteroatom bond at the α-position of the complex (**Scheme 22**). When **87** was treated with cyclohexylamine in the presence of norbornene **40**, benzyl alcohol **88** was produced via the reductive cleavage of the ether bond at the α position. The same result was observed when **89** was treated with cyclohexylamine. Also simple alkenes such as cyclopentene and cyclohexene do not react intermolecularly via this method.[29]

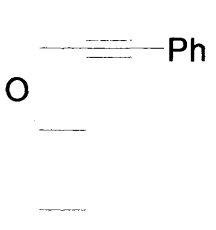
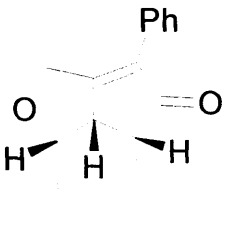
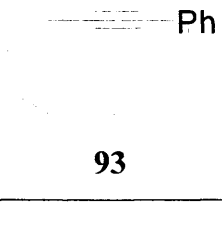
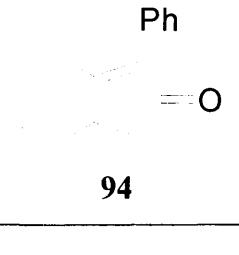
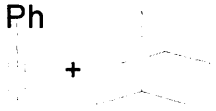
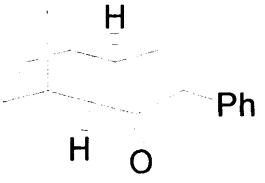
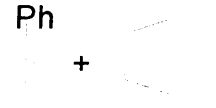
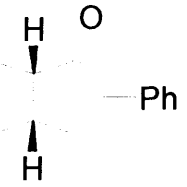
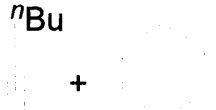
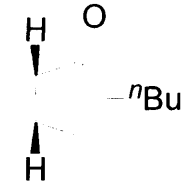


Scheme 22

1.3.4 Sulfides

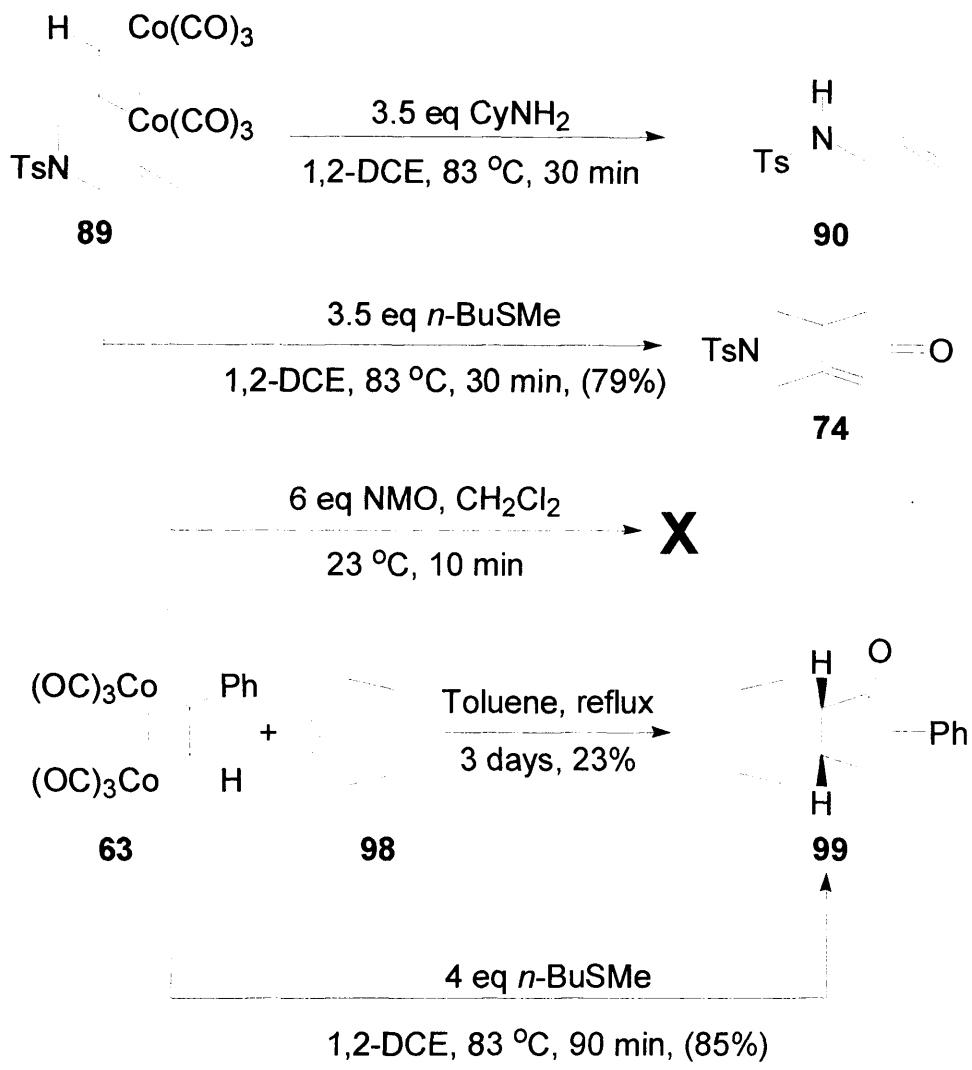
As discussed in the introduction (section 1.2.2.2, p. 20), a suitably positioned sulfur moiety, tethered to the Pauson-Khand cyclisation precursor, increases the reaction efficiency.[30] Sugihara and Yamaguchi have extended this to the use of various sulfides as promoters of Pauson-Khand reaction.[29] Among aryl sulfides, sterically less hindered sulfides such as thioanisole are most efficient at promoting the reaction and sulfides which have electron-donating groups are more effective than those with electron-withdrawing groups. The same steric effect has been observed with dialkyl sulfides. Among these, ones having primary and secondary alkyl groups are more effective than those with tertiary alkyl groups. These observations have led to *n*-butyl methyl sulfide being selected as the promoter of choice. *n*-Butyl methyl sulfide was shown to promote both inter- and intramolecular Pauson-Khand reaction (**Table 6**). Substrates with ether group at the α position cyclised efficiently (entry 1). Substrates with all carbon tether also underwent sulfide promoted Pauson-Khand reaction (entry 2). The cyclisation with reactive alkenes such as norbornene **40** proceeded to give tricyclic compounds in excellent yields (entry 3). Since the sulfide promoted Pauson-Khand reaction proceeded even at 35 °C, the cyclisation of alkenes with low boiling points, such as cyclopentene **64** and cyclohexene **96** was also achieved (entries 4 & 5 respectively).

Table 6. PKR in the presence of *n*-butyl methyl sulfide.

Entry	Substrate(s)	Product	Yield (%)
1	 **91**	 **92**	81[a,b]
2	 **93**	 **94**	94[a,b]
3	 **16** **40**	 **84**	99[b,c]
4	 **16** **64**	 **65**	75[b,c]
5	 **95** **96**	 **97**	68[b,c]

[a] All reactions were carried out in 0.1 M concentration of dicobalthexacarbonyl complex of substrates in 1,2-dichloroethane. [b] Reaction mixture was refluxed at 83 °C. [c] Reaction were carried out in 0.1 M concentration of dicobalthexacarbonyl complex of alkyne in 1,2-dichloroethane. [d] Reaction mixture was heated at 35 °C.

Direct comparison of this method with other Pauson-Khand cyclisation conditions showed it to be the milder method (**Scheme 23**).



Scheme 23

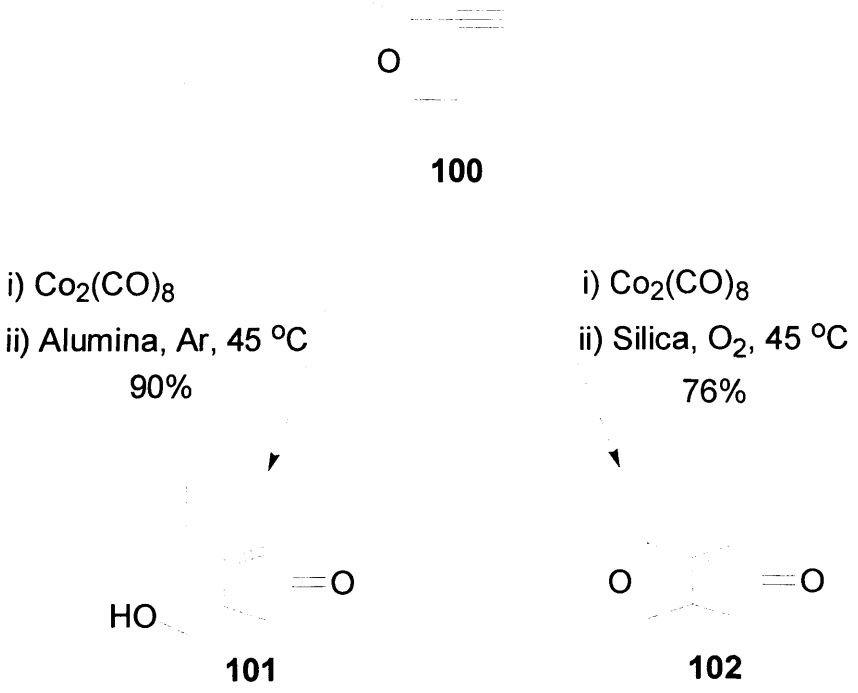
As can be seen from **Scheme 23**, use of cyclohexylamine in the case of enyne **89** leads to a cleavage product **90** whereas the expected product **74** is formed in 79% yield when the sulfide is used as the promoter. Also there is no cleavage of the carbon-heteroatom bond at the α-position. The yield of cyclopentenone **99** is markedly improved to 85% in sulfide promoted reaction relative to 23% in the thermal cyclisation whereas NMO promoted reaction did not lead to any product.

1.3.5 Dry State Adsorption Conditions (DSAC)

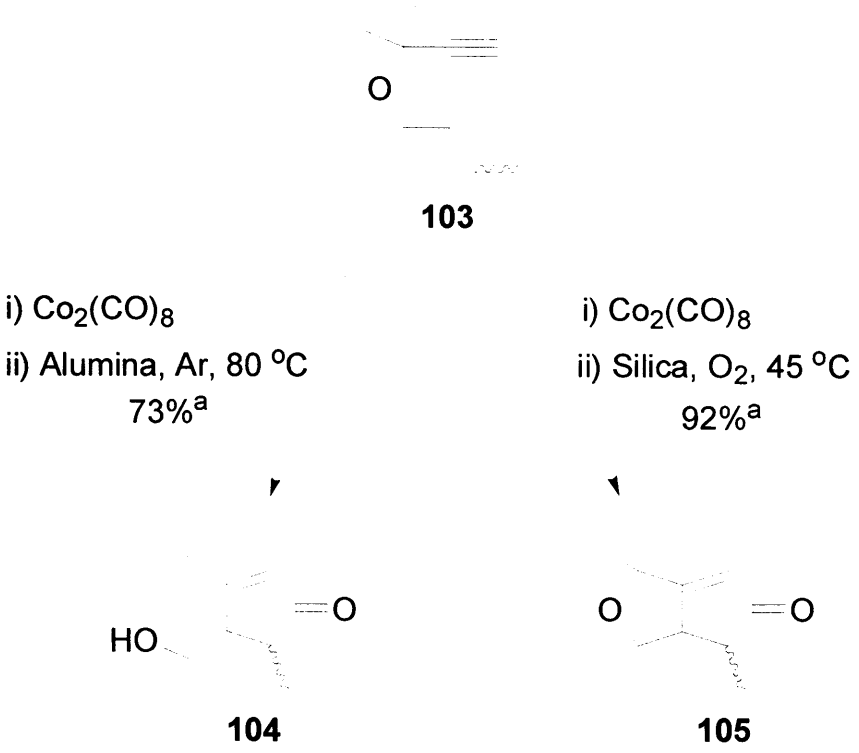
In 1986, Smit and Caple discovered that the intramolecular Pauson-Khand reaction could be accelerated if it was carried out not in solution, but with the substrate adsorbed

onto a chromatographic adsorbent in the absence of solvents and in an atmosphere of oxygen. These conditions are referred to as 'dry state adsorption conditions' (DSAC).[31] A typical procedure involves loading of the dicobalt hexacarbonyl complex of an enyne onto silica followed by removal of solvent then heating in an atmosphere of oxygen.

This method was applied to a series of allyl propargyl ethers containing substituents in various positions. Two examples are illustrated in **Scheme 24** & **25**. Various substrates undergo Pauson-Khand reaction using DSAC and the yields range from 43% to 92%. Use of an argon atmosphere in place of oxygen resulted in the reactant **100** being converted into a monocyclic product **101** and enyne **103** led to **104**. Yields of the reaction under an argon atmosphere range from 40% to 73%.[31]



Scheme 24



[a] 4:1 mixture of stereoisomers, corresponds to isomeric composition of the starting material (*E*:*Z* 4:1).

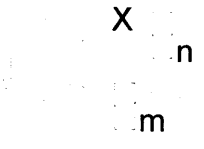
Scheme 25

According to Smit and Caple's studies, various types of silica gels produce comparable results and alumina can also be used as active support for this reaction, the effect being insensitive to the pH of the adsorbent.[32] Silica gels containing about 30% water, dried up or containing 5% water, are rather inactive as media for the reaction and the optimum water content lies between 10 and 20%. The addition of a solvent, such as methanol or hexane, leads to a decrease in the rate and efficiency of the cyclisation.[31]

The catalytic effects of adsorption[32] are attributed to two factors: (i) the preferential stabilisation of the coiled conformation required for the formation of the cyclic intermediate via the interaction of the polar centres (*e.g.* ether centre) of the enyne with the surface hydroxy groups of the adsorbent. This effect, together with the repulsive interactions of the surface with the hydrophobic ends of the precursor would assist in the formation of the cyclic transition state leading to the bicyclic product, and (ii) the promotion of the ligand exchange arising from the interaction of the dicobalt hexacarbonyl complex fragment with the donor centres of the surface.

1.3.6 Molecular Sieves

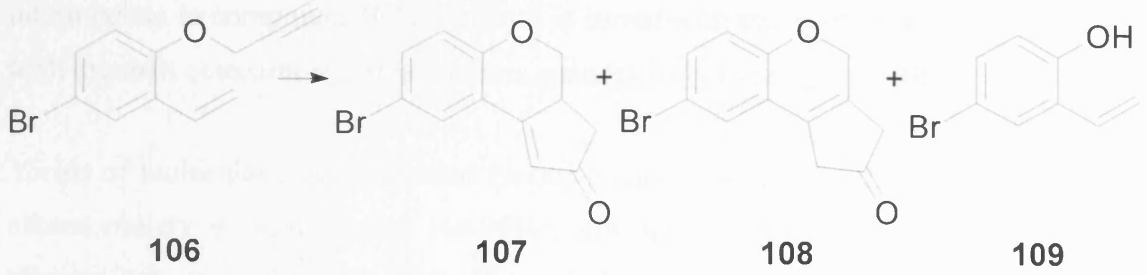
Perez-Castells has reported promotion of intra- and intermolecular Pauson-Khand cyclisation by addition of molecular sieves.[33] The study employed aromatic enynes, of general structure shown in **Figure 2**, as substrates for the cyclisation and it was hoped that the Pauson-Khand cycloaddition would lead to tricyclic products.[34]



n = 1,2
m = 1,2
X = O, NH

Figure 2

Detailed studies on compound **106** in **Scheme 26** showed that use of molecular sieves in refluxing toluene led to an increase in the yield of Pauson-Khand cycloaddition[33]. These aromatic enynes yielded tricyclic enones as products and the major compound was the one where the emerging double bond has isomerised to be conjugated with the aromatic ring as shown in **Scheme 26**, **Table 7**.



Scheme 26

Table 7. Reaction of compound 106 in different conditions

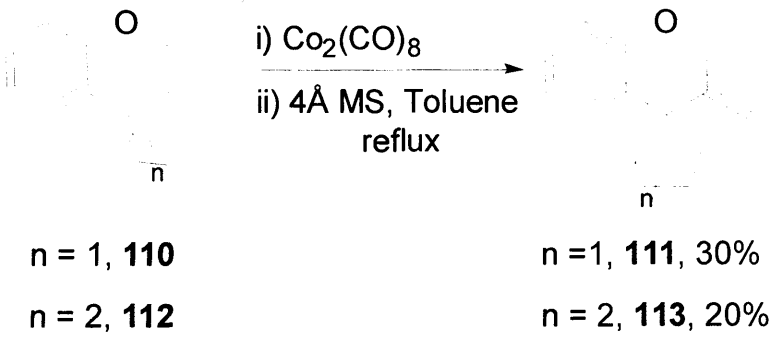
Entry	Solvent	Promoter	T (°C)	Yield (%) 107	108	109
1	CH_3CN	TMANO	-10	7		60
2	CH_3CN	TMANO/4Å MS[a]	-10			65
3	Benzene	TMANO	-10	30		
4	Toluene	TMANO	-10	40		
5	Toluene	TMANO/4Å MS[a]	-10	90	<5	
6	Toluene	4Å MS	112[b]	45	<5	
7	Toluene	none	112	15		
8	Toluene	TMANO/4Å MS[c]	-10	15	75	

[a] Powdered molecular sieves preheated in an oven at 125 °C for 4 h and cooled under argon. [b] No reaction was observed at lower temperatures. [c] Commercial powdered and activated 4Å molecular sieves (8-12 mesh).

Initial studies on compound **106** showed that (i) the more polar the solvent, the more depropargylation is observed. For example with acetonitrile, depropargylation is the major process observed (entry 1 and 2). With less polar solvents such as benzene (entry 3) or toluene (entry 4), no vinyl phenol **109** was observed and the best conversions were achieved with toluene. (ii) TMANO was the only promoter that led to high conversions (entry 5), (iii) raising the temperature to refluxing toluene showed that molecular sieves were able to promote the reaction on their own albeit with lower yield (entry 6), (iv) in the absence of zeolites, the thermal promotion of the reaction only yielded 15% of the compound **107** (entry 7) (v) in addition to favouring the reaction, molecular sieves also modify the double bond isomerisation process. Compound **108** is the major product when less water is present in the reaction mixture (entry 8). It can be considered as the

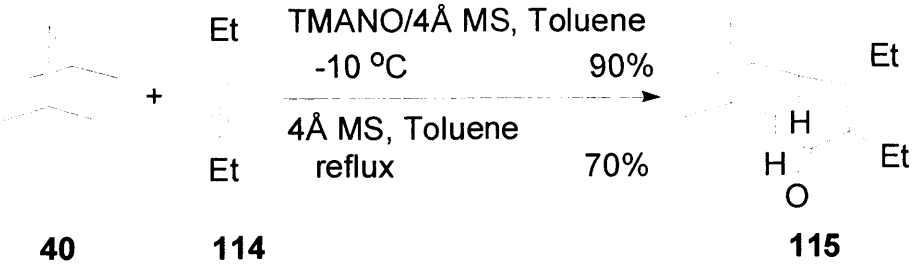
intermediate to compound **107** as when it is stirred with traces of acid or base or simply with dicobalt octacarbonyl, it isomerises quantitatively to compound **107**.

Yields of molecular sieve promoted Pauson-Khand reaction are always good when the alkene moiety is unsubstituted (44-90%), although slightly lower when non-terminal alkynes are used (50-55%). Extension of this reaction to the trisubstituted alkene resulted in failure to obtain Pauson-Khand products; use of TMANO and molecular sieves at -10 °C led to depropargylation, whereas use of molecular sieves in refluxing toluene gave interrupted Pauson-Khand products **111** and **113** (**Scheme 27**). Obtention of these interrupted Pauson-Khand products was attributed to the steric hindrance caused by the substitution in the alkene moiety which prevents carbon monoxide incorporation and led directly to the decomplexation of the cobalt.



Scheme 27

Only one example of intermolecular reaction was reported and is illustrated in **Scheme 28**.



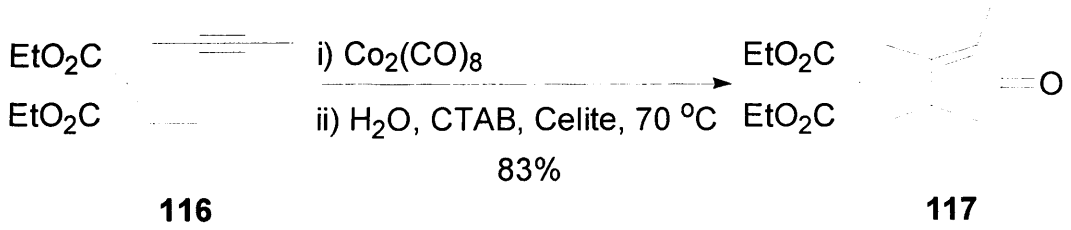
Scheme 28

It was suggested that molecular sieves in this process may act to adsorb the enyne and stabilise a pre-transition state or they may promote ligand exchange.[34]

1.3.7 Aqueous Phase Thermal Pauson-Khand reaction

Krafft has reported the first protocol for stoichiometric thermal Pauson-Khand reaction in water as the only solvent, and in the presence of surfactants as additives, to circumvent the sluggishness of the reaction in water alone.[35]

Preliminary experiments on several enynes led to optimised reaction conditions. An example is shown in **Scheme 29**. The protocol involves heating a dicobalt hexacarbonyl complex of an enyne in water at 70 °C with a small amount of Celite® and 0.6 equivalent of cetyltrimethylammonium bromide (CTAB, a surfactant) under nitrogen. Most reactions went to completion after 18 h of heating. Various other surfactants were tested but the highest yields were obtained with CTAB and cetyltrimethylammonium hydrogen sulfate (CTAHS).



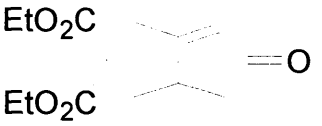
116 **117**

Scheme 29

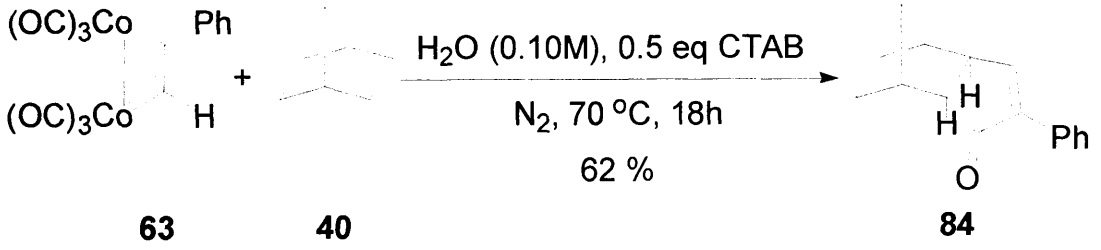
A variety of substrates were screened via the above method to verify the generality of this method. A few examples are illustrated in **Table 8**.

As can be seen from **Table 8**, there was a marginal decrease in the yield from the cyclisation of the enyne with one ester group in the tether (entry 2, 78%) compared to enyne with two ester groups in the tether (entry 1, 83%). A dihydroxylated enyne **120** cyclised to give a good yield of enone **121** (entry 3, 65%). Reaction of enyne **122** bearing the ketal functionality gave moderate yields of the enone **123** (entry 4, 40%). Use of CTAHS as surfactant for the cyclisation of ketal bearing enyne **122** led to loss of the ketal functionality in the resulting enone and **121** was obtained in 62% yield.

Table 8. Aqueous Pauson-Khand reactions with CTAB

Entry	Substrate	Product	Yield (%)
1	 **116**	 **117**	83
2	 **118**	 **119**	78
3	 **120**	 **121**	65
4	 **122**	 **123**	40

One example of intermolecular Pauson-Khand reaction was reported, where the dicobalt hexacarbonyl complex of phenylacetylene **63** and norbornene **40** cyclised in a H_2O-CTAB medium to provide enone **84** in 62% yield (**Scheme 30**).



63 **40** **84**

Scheme 30

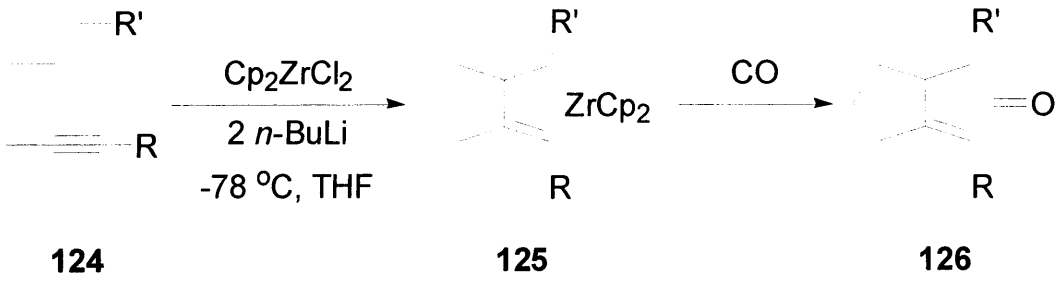
In the same paper it was also reported that cyclisations using tetracobalt dodecacarbonyl $Co_4(CO)_{12}$ provided variable results. In the case of terminal alkynes reductive Pauson-

Khand products were obtained whereas internal alkyne substrates (which are less prone to reductive Pauson-Khand reaction) were not efficiently converted to their corresponding enones.[35]

1.3.8 Pauson-Khand reaction with metals other than Cobalt

Other metals apart from cobalt can mediate Pauson-Khand-type reactions. Although these have found best use in catalytic version, as will be discussed later, the stoichiometric reaction has been performed with zirconium[36] iron[37] molybdenum and tungsten[38] palladium[39] and with varying degrees of success.

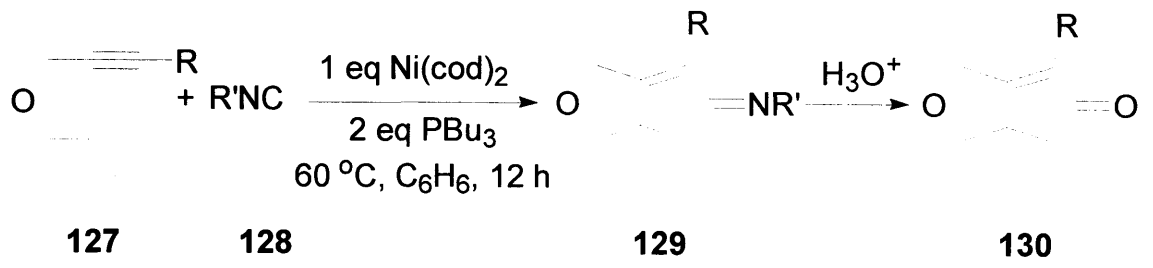
Negishi has reported a zirconium promoted intramolecular variation of the Pauson-Khand reaction involving a zirconacycle intermediate **125** (**Scheme 31**).[36] Carbonylation occurs under an atmosphere of CO to afford cyclopentenone as shown in **Scheme 31**.



Scheme 31

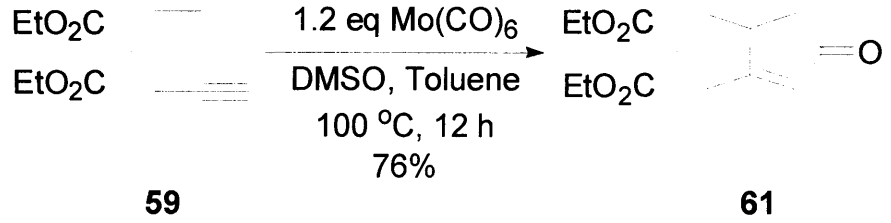
When an isocyanide is used instead of CO, the reaction gives an iminocyclopentene, which can be hydrolysed to a bicyclic enone.

Tamao[40] has used bis(cyclooctadienyl)-nickel in the presence of an isocyanide **128**, a carbon monoxide equivalent, to convert enynes of type **127** to bicyclic iminocyclopentenes **129** which can be hydrolysed to the corresponding cyclopentenones **130**, as shown in **Scheme 32**.



Scheme 32

$M(CO)_6$ (M = Mo, W) has been used in the presence of excess DMSO to yield cyclopentenones.[38] The Pauson-Khand reaction of enyne **59** under these conditions yielded cyclopentenone **61** in 76% yield (**Scheme 33**). Intermolecular reactions were not as effective as the intramolecular version.



Scheme 33

1.4 Catalytic Pauson-Khand reaction

Only catalytic Pauson-Khand reaction fulfils the criterion of atom economy. The use of stoichiometric amounts of the transition metal is not acceptable commercially. It is not surprising therefore, that several research groups have more recently focused on developing catalytic variants.[5] Although the catalytic Pauson-Khand reaction was reported as early as 1973, it was confined to strained reactive alkenes *e.g.* norbornene and norbornadiene, and required an excess of alkyne compound.[8a] Early work with gaseous alkynes suggested that the process could be carried out in a catalytic fashion by stirring a mixture of alkene and *ca.* 10 mol% $Co_2(CO)_8$ in an inert solvent under a 1:1 alkyne/CO atmosphere. The success of these attempts depended on a continuous supply of excess alkyne being able to trap and recycle reactive cobalt-containing fragments.[8a]

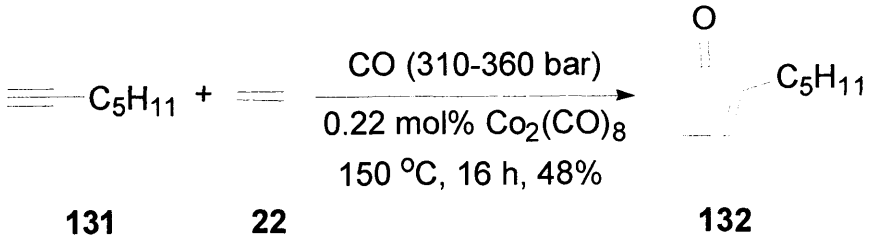
There has been a marked increase in interest to develop catalytic Pauson-Khand reaction by several groups working in this area, especially during the 1990s. Nowadays the catalytic variations have been successful in various examples of inter- and intramolecular Pauson-Khand reactions.

Methods that have been developed for the catalytic Pauson-Khand reaction are typically based on a combination of one or more of the following premises: i) *in situ* generation of the active cobalt carbonyl species, ii) preservation of the active cobalt carbonyl species, iii) preservation of the intermediate complexes, and iv) facilitation of decarbonylation, hence increased alkene complexation rate. Furthermore, catalysis in the Pauson-Khand reaction is best achieved in reactions that are carried out under an atmosphere of carbon monoxide so that regeneration of the active catalyst is possible.[41]

The catalytic Pauson-Khand reactions reported to date involve i) the use of carbon monoxide atmosphere, ii) modified cobalt complexes, iii) light induction, or iv) complexes of other metals such as titanium, ruthenium or rhodium.

1.4.1 Use of a carbon monoxide (CO) atmosphere

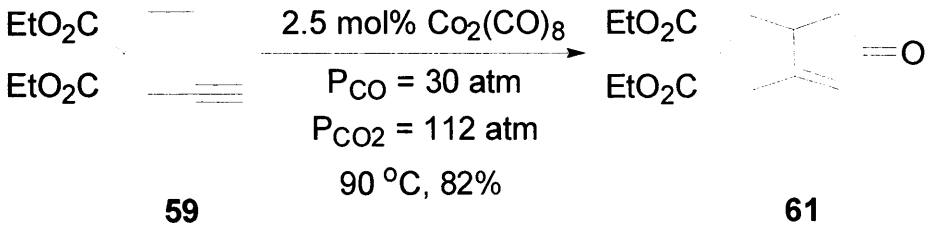
Rautenstrauch *et al.*[42] showed in their 1990 synthesis of the dihydrojasmonate precursor **132** that catalytic Pauson-Khand reactions are possible if high CO pressure and high temperature are used.



Scheme 34

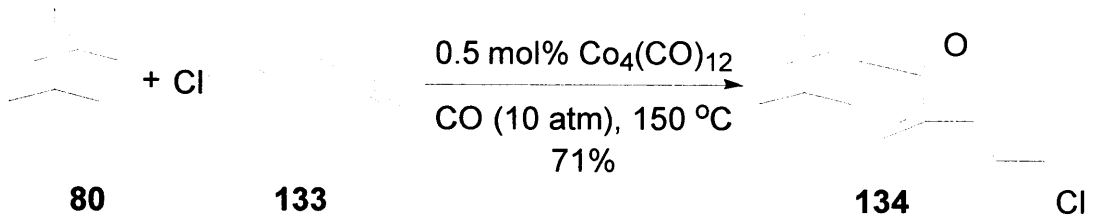
Modifications to the reaction conditions and/or the cobalt metal catalyst have proven to be effective in increasing the yields in catalytic Pauson-Khand cycloadditions.

In 1997 Jeong[43] reported the use of supercritical CO_2 fluid in catalytic Pauson-Khand reaction. The reactions were performed in supercritical CO_2 by charging a cylindrical stainless steel reactor with a catalyst and enyne followed by pressurising with CO and CO_2. According to their study, high reaction temperature (90-100 °C) and high CO pressure (15-30 atm) were required. The reaction was effective in inter- and intramolecular reactions, however there were only 4 intra- and 2 intermolecular examples and thorough studies are required. An intramolecular reaction of enyne **59** is illustrated in **Scheme 35**.



Scheme 35

Chung and coworkers[44] have reasoned that the problem with catalytic thermal Pauson-Khand reaction may be the formation of $Co_4(CO)_{12}$ during the reaction which may cause a dead end. They suggested that at high pressure of CO and at high temperature most cobalt carbonyls exist as $Co_2(CO)_8$ instead of $Co_4(CO)_{12}$. They carried out the Pauson-Khand reaction using $Co_2(CO)_8$ and $Co_4(CO)_{12}$ under a high pressure of CO and at high temperature. The optimum conditions were for a reaction at 150 °C under 10 atm of CO. In general at less than 5 atm of CO the reaction did not proceed well for most substrates in the study. The practical lower limit of temperature seemed to be about 60-79 °C. The scope of the reaction was examined in both inter- and intramolecular fashion. The reaction of compound **59** using 1 mol% of $Co_4(CO)_{12}$ yielded 92% of the product **61**. An intermolecular example is shown in **Scheme 36**.

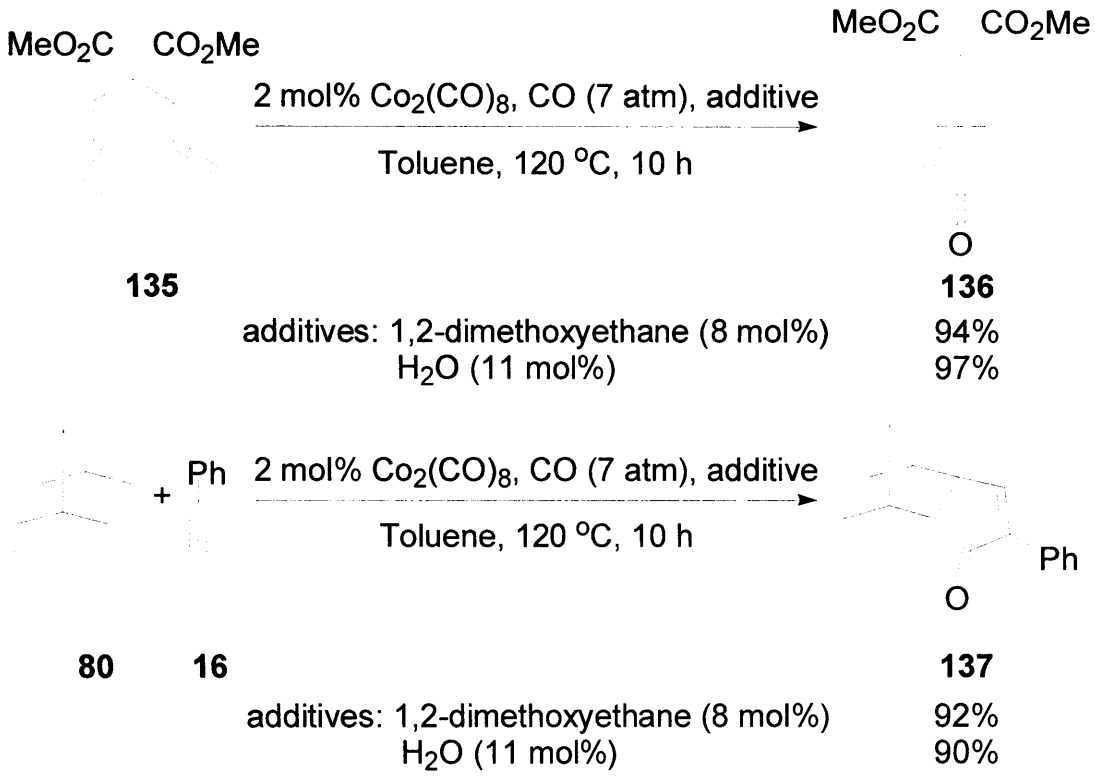


Scheme 36

This catalytic system has been shown to be quite effective for terminal alkynes having aryl, alkyl, alkyl chloride, alcohol and alkenes as substituents. Compared to intermolecular reactions, intramolecular reactions need more $Co_4(CO)_{12}$ (1 mol% compared to 0.5 mol%) and longer reaction times.

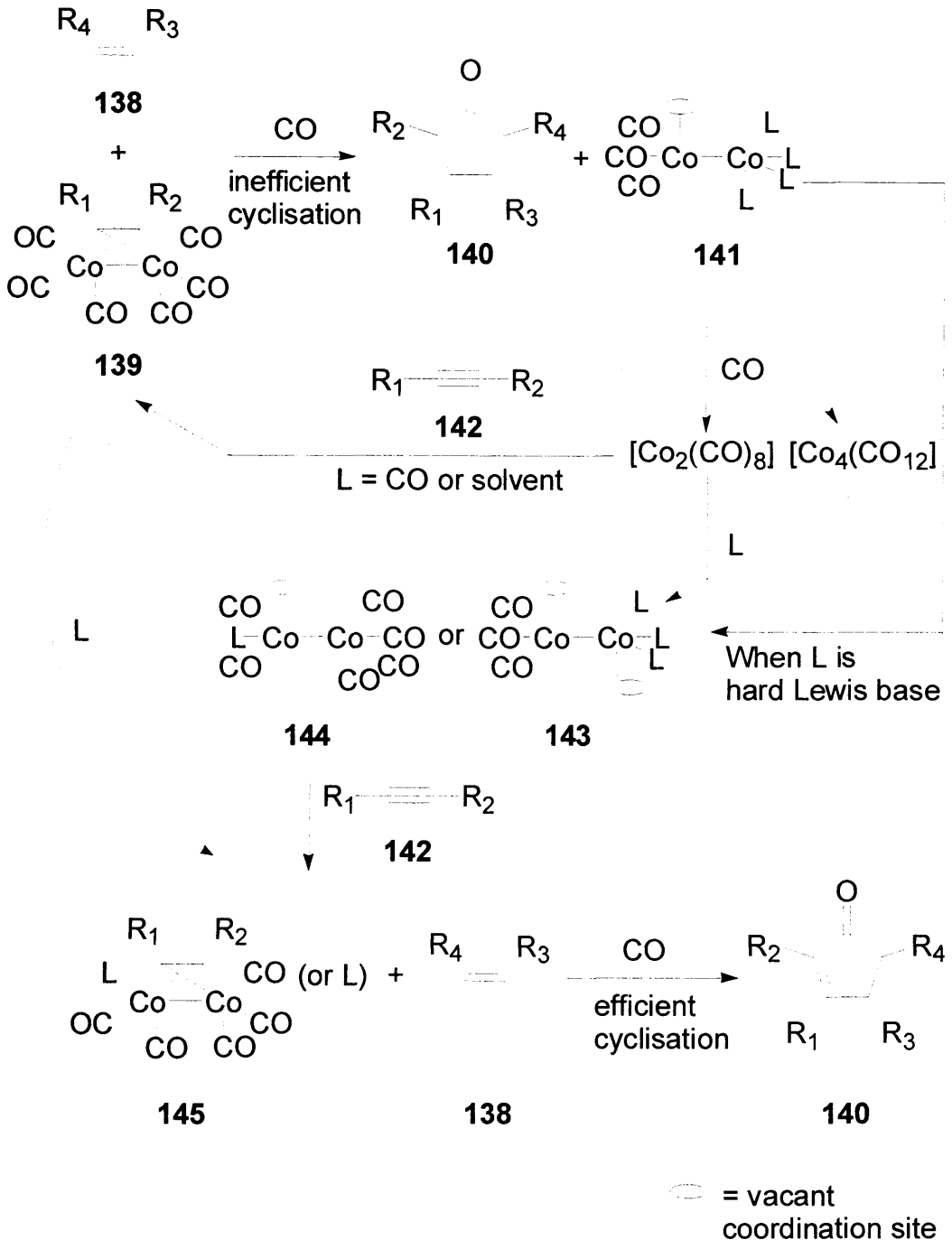
Sugihara has reported that both the inter- and intramolecular catalytic Pauson-Khand cycloaddition can be promoted using "hard" Lewis bases.[45] He reasoned that "hard" Lewis bases on low-valent organotransition metal complexes labilise the existing ligand. This effect facilitates the ligand substitution reaction and sometimes makes the coordinating ligands reactive. In the case of alkyne or enyne dicobalt hexacarbonyl complexes, this labilising effect would lead to more facile co-ordination of the alkene onto a vacant site on cobalt.

Initial studies on compound **135** (**Scheme 37**) showed that cyclohexylamine, which was the best promoter for stoichiometric Pauson-Khand reaction, was not effective under catalytic conditions.[46] On the contrary, secondary and tertiary amines allowed catalytic cyclisation and *N,N*-diisopropylethylamine was the most effective among investigated amines. These studies showed that a sterically bulky or less electron-donating "hard" Lewis base can activate dicobalt octacarbonyl without decomposition. Lewis bases such as *N,N*-diisopropylethylamine, benzyl alcohol, 1,4-dioxane, 1,2-dimethoxyethane (DME), and water catalysed the cyclisation of **135** in good yields. DME and water gave comparable results. Among these activators, DME and water seemed to be the most effective. DME can act as the activator of dicobalt octacarbonyl in a narrow range of temperature (60-70 °C) without decomposing the catalyst. The amount of additive is critical and a pressure of CO of about 7 atm is also necessary for efficient catalysis. This method is effective for both inter- and intramolecular reactions and example of each is shown in **Scheme 37**.



Scheme 37

A proposed mechanistic hypothesis for this catalysis[45] is shown in **Scheme 38.**



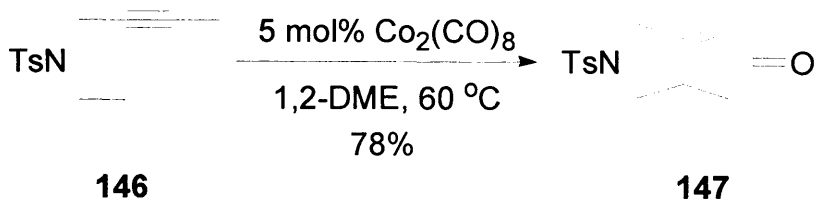
Scheme 38

Under the original conditions, coordinatively unsaturated cobalt carbonyl complex **141** is produced after the cyclisation. When the reaction is carried out under CO atmosphere, the complex **141** may transform into $Co_2(CO)_8$ or in the presence of alkyne to dicobalt hexacarbonyl complex of alkyne **139**, therefore a catalytic amount of $Co_2(CO)_8$ is theoretically required to complete the cyclisation. However the turnover number of the reactions carried out in this fashion have not been satisfactory. The reasons are

considered as follows: (i) feasibility in transformation of the coordinatively unsaturated dicobalt carbonyl complex **141** into $Co_4(CO)_{12}$ which is considered as inactive in the catalytic PKR, (ii) retardation in formation of complex **139** and coordination of an alkene to **139** under CO atmosphere, and (iii) inefficiency of the PKR under the original conditions. When the reaction is carried out in the presence of "hard" Lewis bases $Co_4(CO)_{12}$ may be transformed into $Co_2(CO)_8$ or the coordinatively unsaturated cobalt complexes **143** and **144**. Complexes **143** and **144**, are responsible for the catalytic action in this reaction. The electron-donating effect of "hard" Lewis bases may stabilise these coordinatively unsaturated complexes. In addition once complex **145** is produced, the cyclisation may be facilitated as seen in the primary amine promoted stoichiometric Pauson-Khand reaction.

Sugihara in this paper postulated that the course of reaction differed for stoichiometric and catalytic Pauson-Khand reaction, based on two findings in this study. Firstly that cyclohexylamine is an efficient promoter of stoichiometric Pauson-Khand reaction but it does not promote catalytic Pauson-Khand reaction at all and secondly that water does not promote stoichiometric Pauson-Khand reaction, however it effectively catalysed the catalytic Pauson-Khand reaction.

Livinghouse determined that the cobalt catalysed intramolecular Pauson-Khand reaction could be promoted thermally under 1 atm of CO pressure.[47] Cyclisation studies showed that a very narrow thermal window (60-70 °C) exists for the efficient catalysis. Typical conditions involve stirring the enyne of interest in degassed 1,2-DME in the presence of high purity 5 mol% $Co_2(CO)_8$ at 60 °C under 1 atm of CO for 12-15 hours. Reaction yields were high and ranged from 77-86%. Example of an intramolecular reaction is shown in **Scheme 39**. In some cases (e.g., disubstituted alkenes) 7.5 to 10 mol% $Co_2(CO)_8$ was required.

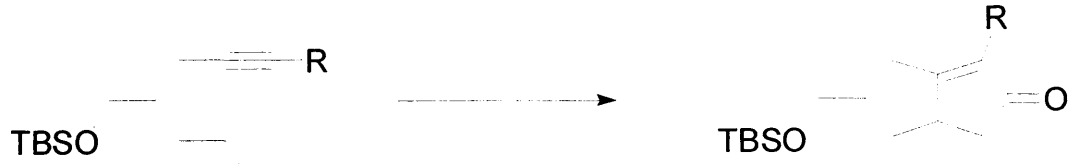


Scheme 39

Krafft[48] has reported a modification of the Livinghouse procedure in which further purification of $Co_2(CO)_8$ is not necessary. They reported that when carefully base washed glassware was used, the catalytic reaction proceeded to completion in most cases using 10 mol% of unpurified $Co_2(CO)_8$ in 1,2-DME under a blanket of CO.

They also reported limitations of the Livinghouse procedure when internal or sterically hindered alkynes were used. In order for these to cyclise 30-60 mol% of the catalyst was required. Krafft used cyclohexylamine in their catalytic variation of Livinghouse process[47] to obtain enhanced yields in most cases. A typical procedure involved using 5-10 mol% of $Co_2(CO)_8$ and 20 mol% of $CyNH_2$ with heating at 70 °C. Lower yields of products were obtained in THF or toluene compared to 1,2-DME.

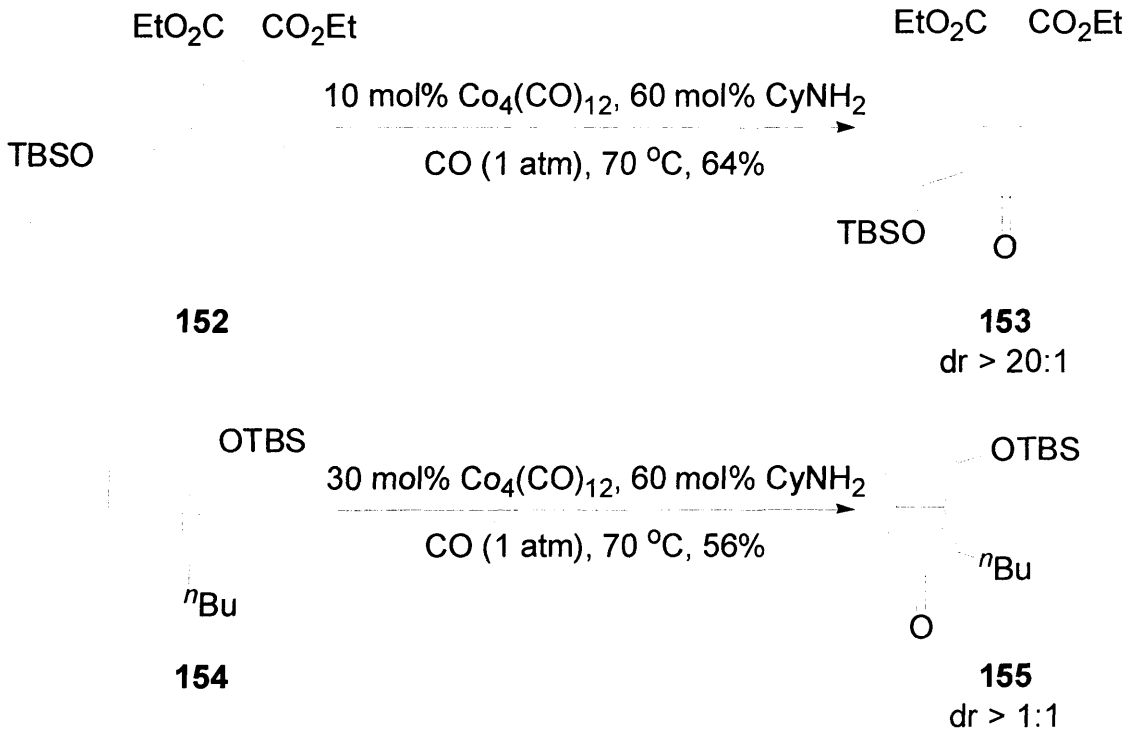
The examples in **Scheme 40** illustrate that when a terminal alkyne (R = H, **148**) is used, 5 mol% of the catalyst and 20 mol% of $CyNH_2$ are required whereas when an internal alkyne (R = ^{n}Pr, **150**) is used 30 mol% of the catalyst and 60 mol% of $CyNH_2$ are required.



When R = H,(**148**) 5:20 mol% $Co_2(CO)_8$: $CyNH_2$ **149**, 89% (dr 1:1)
R = ^{n}Pr (**150**), 5:20 mol% $Co_2(CO)_8$: $CyNH_2$ **151**, 8% (dr 1:1)
R = ^{n}Pr (**150**), 30:60 mol% $Co_2(CO)_8$: $CyNH_2$ **151**, 95% (dr 1:1)

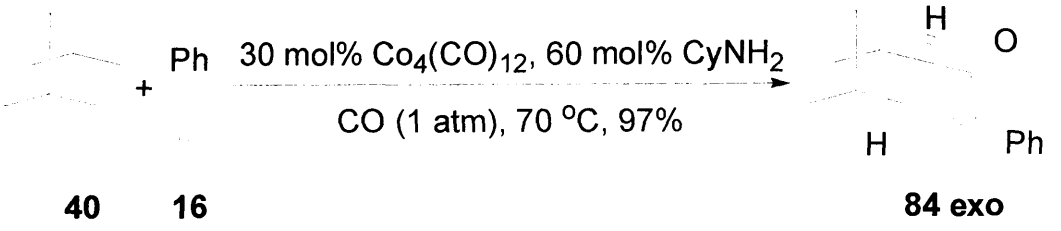
Scheme 40

Krafft[49] has also reported that a catalytic amount of tetracobalt dodecacarbonyl $Co_4(CO)_{12}$ could be used in conjunction with cyclohexylamine to catalyse Pauson-Khand reaction at 1 atmosphere pressure of CO. Reactions were typically carried out at a substrate concentration of 0.05 M in DME using 10 mol% of $Co_4(CO)_{12}$ and 60 mol% of $CyNH_2$ under a CO atmosphere at 70 °C. Two examples are illustrated in **Scheme 41**.



Scheme 41

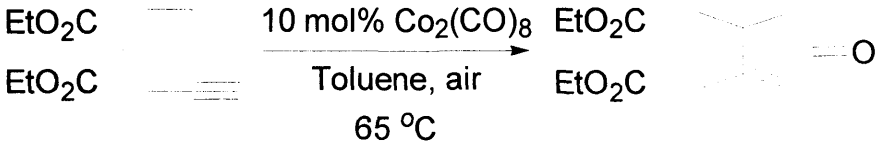
Lower yields were obtained with enynes containing disubstituted alkenes (*e.g.* **152**). Also enynes bearing internal alkynes or which are sterically hindered need a higher catalyst loading of approximately 30 mol% (*e.g.* **154**). An intermolecular version was also reported as shown in **Scheme 42**.



Scheme 42

Krafft and coworkers[49] have discounted the assumption that $Co_4(CO)_{12}$ is inactive towards the Pauson-Khand reaction under mild conditions such as 1 atmosphere of CO and 70 °C. Krafft has postulated that $Co_4(CO)_{12}$ under these conditions undergoes disproportionation into $Co_2(CO)_8$ or a similar catalytically active cobalt species. They presume that $CyNH_2$ encourages disproportionation and promotes preservation of catalytically active cobalt species.

Recently Perez-Castells and co-workers[50] have reported a new protocol for the catalytic Pauson-Khand reaction induced by molecular sieves which had been pretreated with CO. Enyne **59** was submitted to three reactions in air atmosphere with 10 % dicobalt octacarbonyl: blank reaction, addition of molecular sieves, and addition of molecular sieves which had been heated to 200 °C and cooled under carbon monoxide (**Scheme 43**).



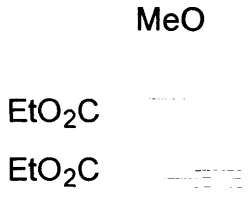
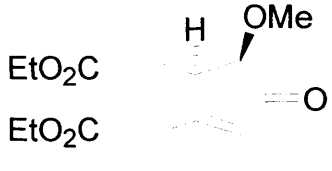
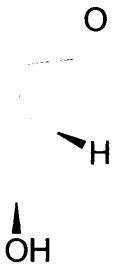
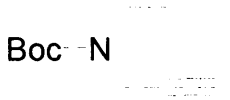
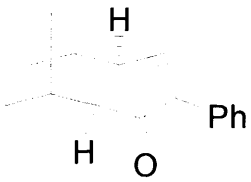
59 **61**

Without MS:	15%
With MS:	30%
With MS pretreated with CO:	65%

Scheme 43

The results show a significant increase in yield with sieves, reaching 65 % with pre-treated zeolites. After optimisation studies, the best results were obtained when reaction was carried out in toluene with molecular sieves (preheated to 125 °C for 4 h and cooled under argon), under carbon monoxide atmosphere and 10 mol% dicobalt octacarbonyl. The results for some of the substrates are shown in **Table 9**.

Table 9. Catalytic PKR in the presence of molecular sieves

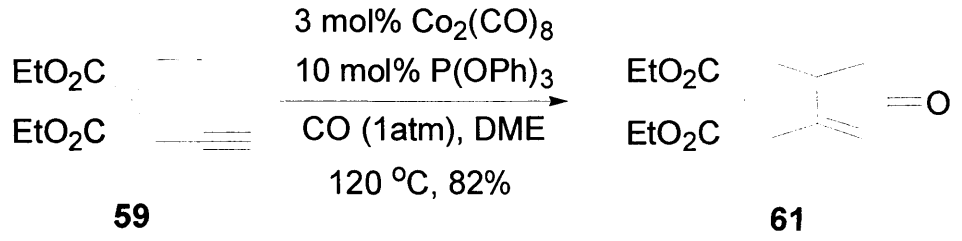
Entry	Substrate	Product	Yield (%)
1	 **156**	 **157**	90
2	 **158**	 **159**	70
3	 **160**	 **161**	70
4	 **40** **16**	 **84**	70

The authors have postulated that molecular sieves improve the conversion of the catalytic Pauson-Khand reaction, probably due to their ability to adsorb and keep carbon monoxide.

1.4.2 Use of modified cobalt complexes

Various catalytic versions of the Pauson-Khand reaction where modified cobalt complexes have been employed have been reported in the literature and below is a summary of the most useful variations to date.

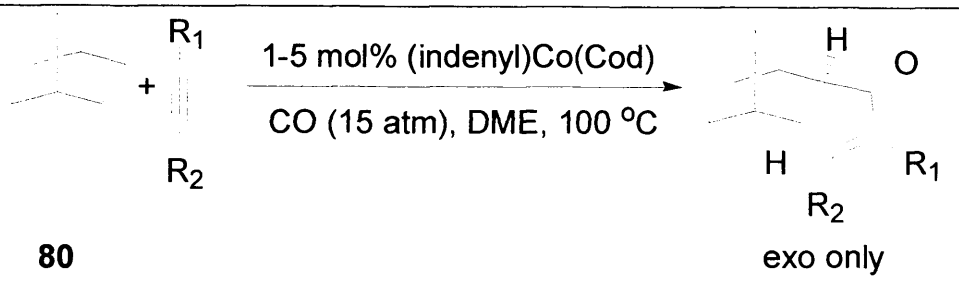
Jeong[51] reported that one of the main obstacles to overcome in the development of the catalytic process were the formation of metal clusters or other inactive metal carbonyl species. They felt that use of other ligands might stabilise the active cobalt intermediates. Jeong has reported a catalytic conversion of enynes into cyclopentenones employing phosphites as coligands.[51] Use of triphenyl phosphite (10 mol%) as a coligand with dicobalt octacarbonyl (3 mol%) gave 51-94% yields in seven examples of intramolecular cycloaddition. An example is illustrated in **Scheme 44**.



Scheme 44

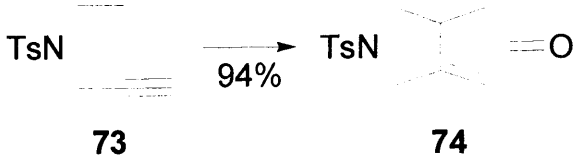
Jeong and Chung[52] have also reported the use of a 1,5-cyclooctadiene (indenyl) cobalt (I) complex for the catalysis of both inter- and intramolecular cyloadditions. High yields (53-97%) were reported for intermolecular cycloadditions of norbornene and norbornadiene with a variety of alkynes and 64-94% yields were reported for two intramolecular versions. In these examples 1-2 mol% of catalyst with high CO pressure (15 atm) at 100 °C were the standard conditions. **Table 10** shows the reaction of norbornadiene **80** with various alkynes, using these reaction conditions. Terminal alkynes generally gave good yields of cyclopentenones (entries 1-4) whereas alkyne conjugated to a carbonyl (entry 5) did not give any corresponding product. A free hydroxyl group was shown to be compatible with the reaction conditions (entries 3 & 4). Disubstituted alkynes (entries 6 & 7) were not such good substrates for this reaction as terminal alkynes.

Table 10. Catalytic PKR using (indenyl)Co(Cod)



Entry	Substrate	R_1	R_2	Product Yield (%)
1	**16**	Ph	H	**137**, 93
2	**162**	$(CH_2)_5CH_3$	H	**163**, 95
3	**164**	$C(CH_3)_2OH$	H	**165**, 95
4	**166**	CH_2CH_2OH	H	**167**, 96
5	**168**	CO_2Et	H	**169**, 0
6	**170**	Ph	Ph	**171**, 59
7	**172**	Ph	Me	**173**, 53

An intramolecular reaction was also tested with 2 mol% of the catalyst and reaction of compound **73** as shown in **Scheme 45** yielded 94% of the product **74**.



Scheme 45

Sugihara[53] has reported the use of methylidynetricobalt nonacarbonyl as a catalyst. Alkylidynetricobalt nonacarbonyl clusters (**174** in **Figure 3**) are easily prepared by the reaction of dicobalt octacarbonyl with trihaloalkanes. They are more stable against autooxidation than the parent dicobalt octacarbonyl and have a similar structure to dicobalt hexacarbonyl complex of alkynes (**175** in **Figure 3**) in which one carbon vertex of the tetrahedron is replaced with a $Co(CO)_3$ unit.

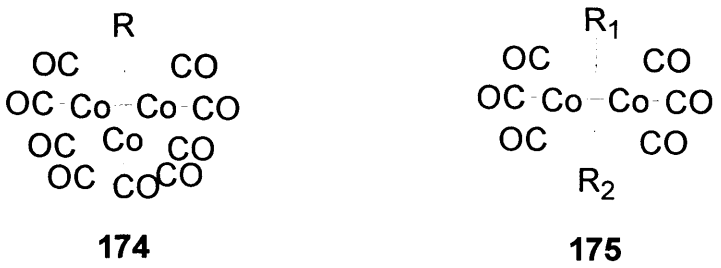
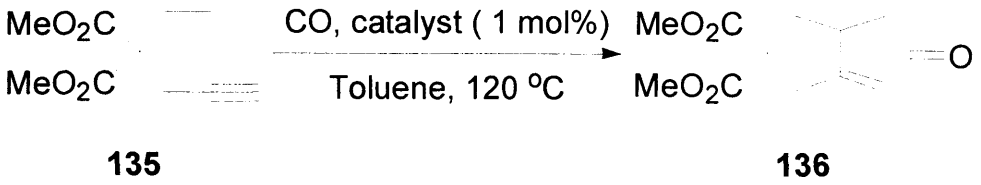


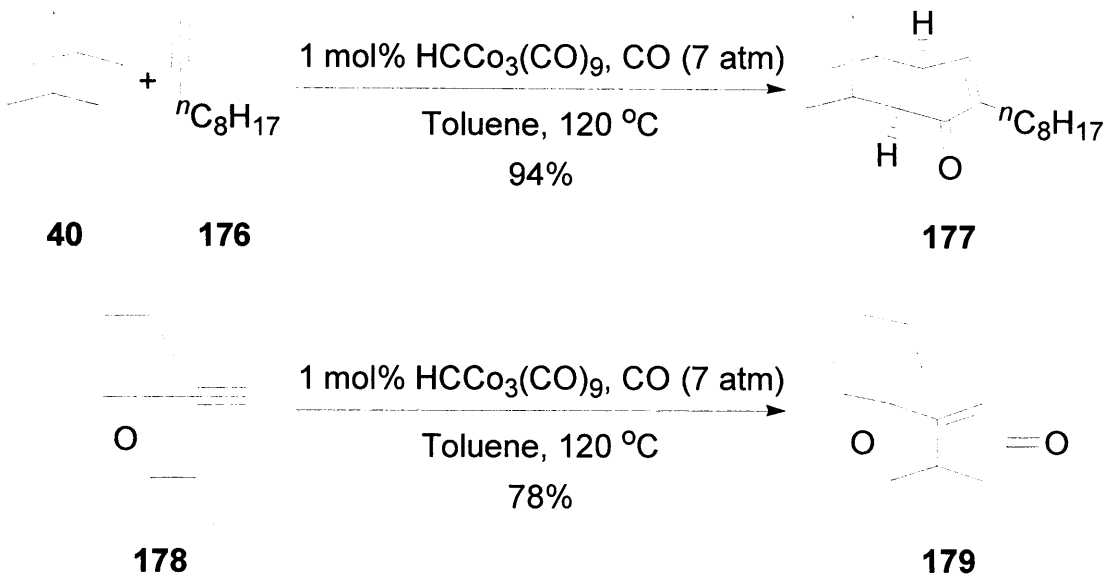
Figure 3

Initial studies were carried out on the reaction in **Scheme 46** below.



Scheme 46

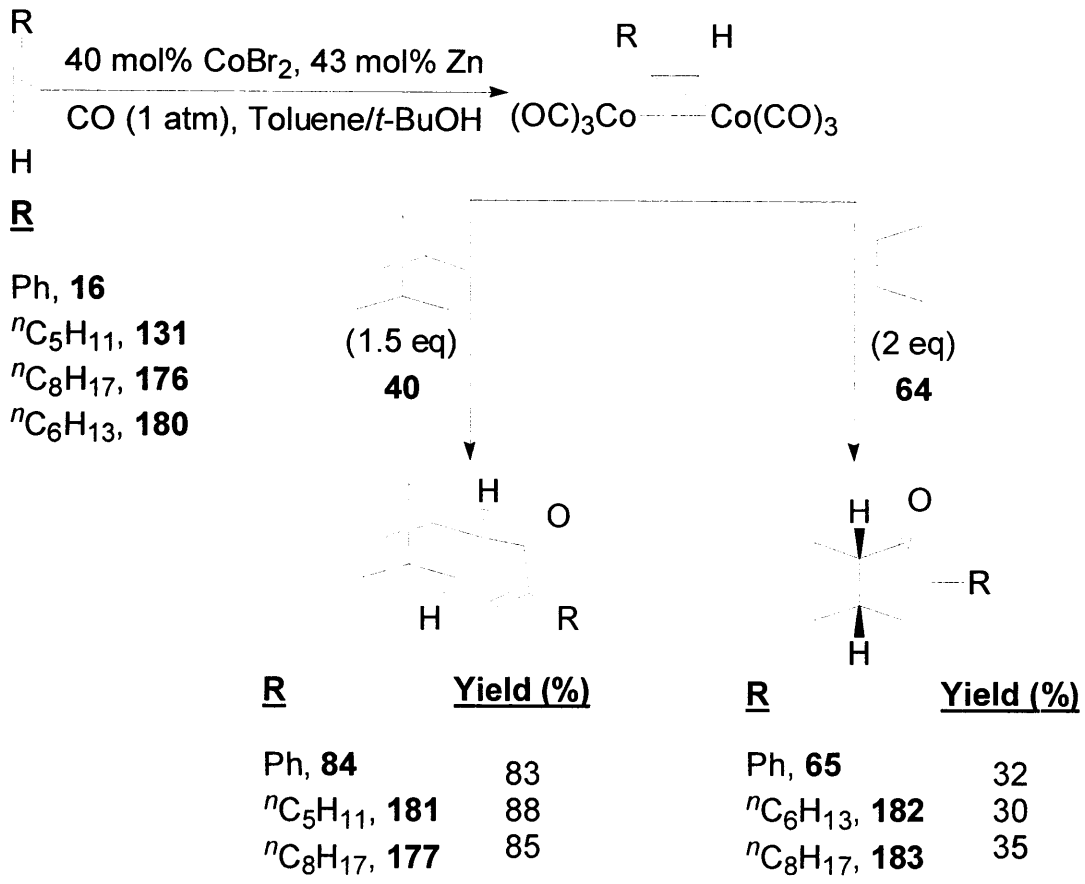
These studies showed that when dicobalt octacarbonyl was used in the absence of an activator, only low conversions were achieved. In contrast methylidynetricobalt nonacarbonyl (R=H in **174**, **Figure 3**), itself efficiently catalysed the reaction and did not need an activator. Clusters with relatively small substituents on the carbon unit (R = Cl, CH_3, $COOC_2H_5$) catalysed the desired cyclisation, while ones with aromatic substituents (R=C_6H_5) were detrimental to the catalysis. The best results were obtained by using the parent cluster methylidynetricobalt nonacarbonyl (R=H in **174**, **Figure 3**). Toluene was the solvent of choice and also 7 atm of CO was the optimum pressure required under these conditions. Examples of inter and intramolecular Pauson-Khand reaction catalysed by methylidynetricobalt nonacarbonyl (R=H in **174** , **Figure 3**) are shown in **Scheme 47**.



Scheme 47

Studies on a series of substrates have shown that intramolecular reaction takes place independent of the substituents on the alkyne moiety. On the other hand, the number of substituents on the alkene is important as trisubstituted alkenes did not undergo the cyclisation reaction and led to recovery of starting material. Additionally an increase in tether length, from 3 to 4 carbon atoms, was detrimental to the cyclisation and led to low conversions. Heteroatom containing compounds such as tosylamides or ethers also cyclised effectively. Intermolecular Pauson-Khand reaction was also possible in the presence of norbornene and norbornadiene in combination with a terminal alkyne[53]. The air stability and ease of preparation of the cluster are noted as the highlight of this procedure.

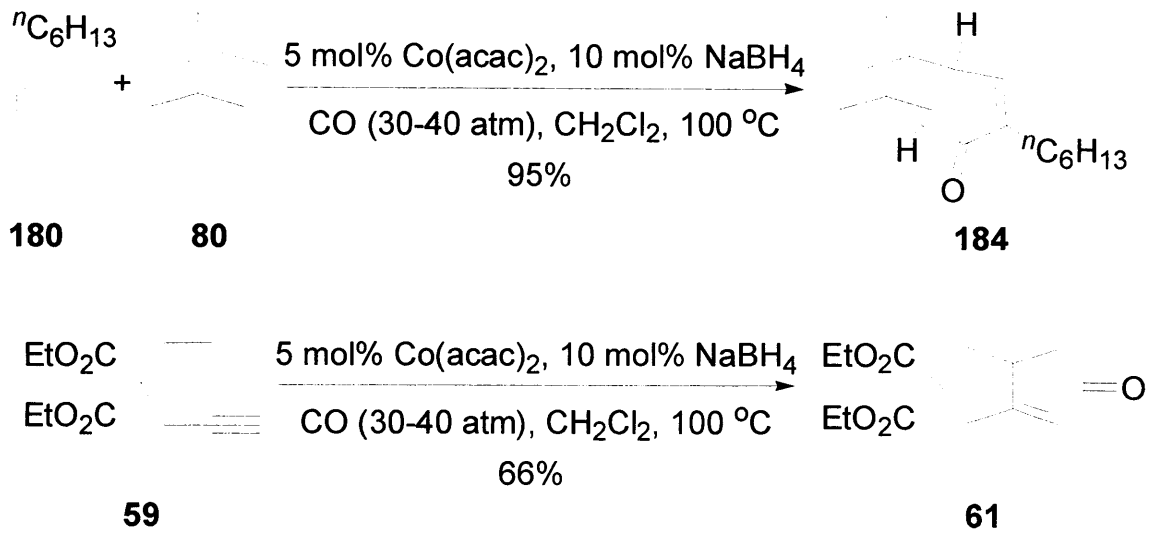
Periasamy[54] has reported that Pauson-Khand reaction can be readily carried out with an alkyne complex generated *in situ* using a sub-stoichiometric amount of $CoBr_2$ (40 mol%) and Zn (43 mol%), in toluene / *t*-BuOH at 1 atmosphere pressure of CO. Their results are summarised in **Scheme 48**.



Scheme 48

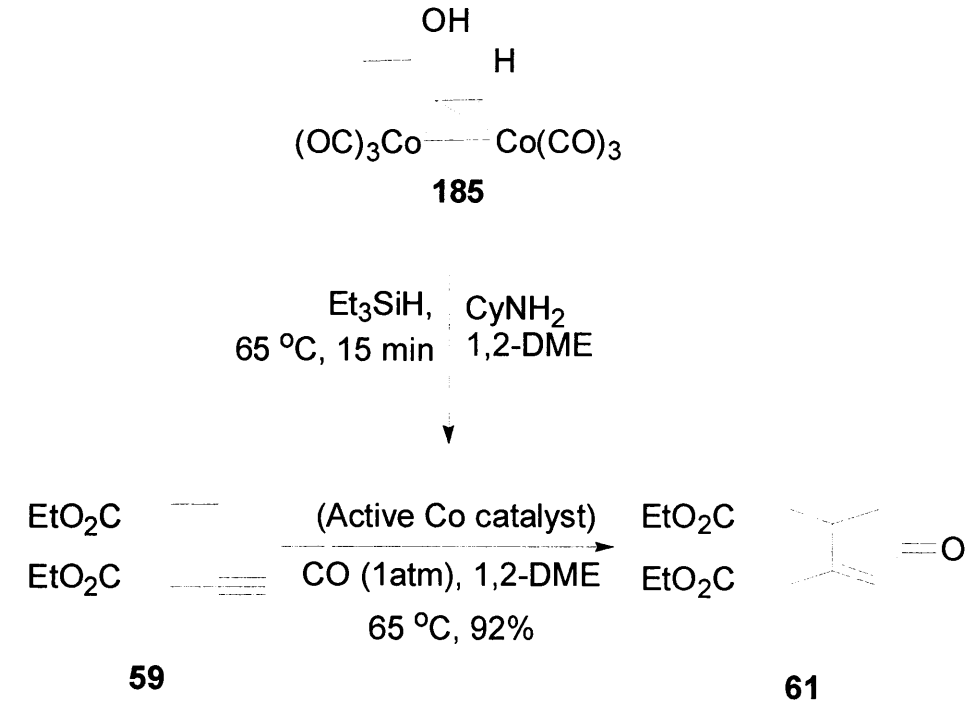
As shown in **Scheme 48**, reactions with less strained alkenes such as cyclopentene (**64**) proved less efficient.

Chung[55] reported that a combination of $Co(acac)_2$ and $NaBH_4$ in catalytic amount effectively promoted both inter- and intramolecular cycloaddition. It is postulated that a system of this reagent under pressure of CO produces $Co_2(CO)_8$. A typical procedure involves 5-10 mol% of $Co(acac)_2$ and 10-20 mol% of $NaBH_4$ under 30-40 atm of CO at 80-100 °C. The yields of the reactions ranged from 30-95%. An inter- and intramolecular example are shown in **Scheme 49**.



Scheme 49

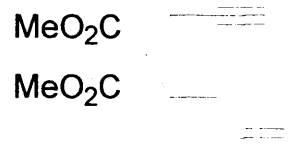
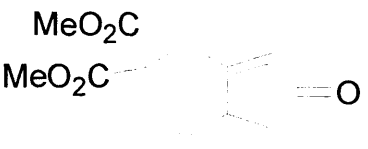
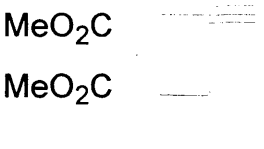
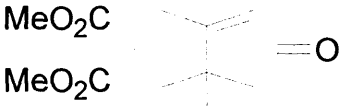
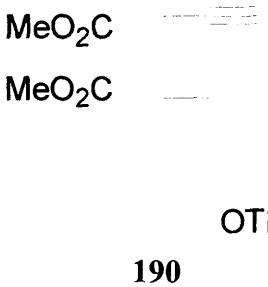
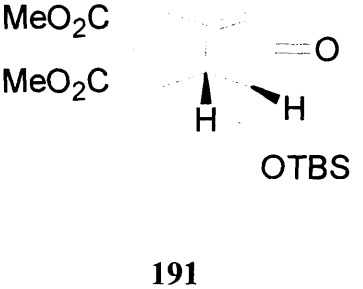
Livinghouse and Belanger have found that some alkyne dicobalt hexacarbonyl complexes can serve as a source of an active cobalt catalyst for carbonylative enyne cyclisations and act as convenient substitutes for the realtively labile $Co_2(CO)_8$ in the catalytic thermal Pauson-Khand reaction[56]. A subsequent *in situ* reduction of the initial alkyne complex with Et_3SiH was used to generate active cobalt catalyst. A series of $Co_2(CO)_6$-alkyne complexes (*e.g.*, complexes of: $HO(CH_3)_2CC{\equiv}CH$, $PhC{\equiv}CH$, $PhC{\equiv}CPh$, $TMSC{\equiv}CTMS$, $HOCH_2C{\equiv}CH$, $HOCH_2C{\equiv}CCH_2OH$ and $MeO_2CC{\equiv}CCO_2Me$) were screened in combination with Et_3SiH as $Co_2(CO)_8$ surrogates in the catalytic Pauson-Khand reaction involving enyne **59** (**Scheme 50**). Of the various alkyne derivatives examined, the $Co_2(CO)_6$ complexes of 2-methyl-3-butyn-2-ol and phenylacetylene were virtually identical as sources of highly active catalyst. The $Co_2(CO)_6$ complex of 2-methyl-3-butyn-2-ol (**185**) was chosen as catalyst source due to its crystalline nature, shelf stability, ease of preparation and high decomplexation rate in the presence of Et_3SiH. Addition of cyclohexylamine to the reaction mixture led to improved yields in many cases.



Scheme 50

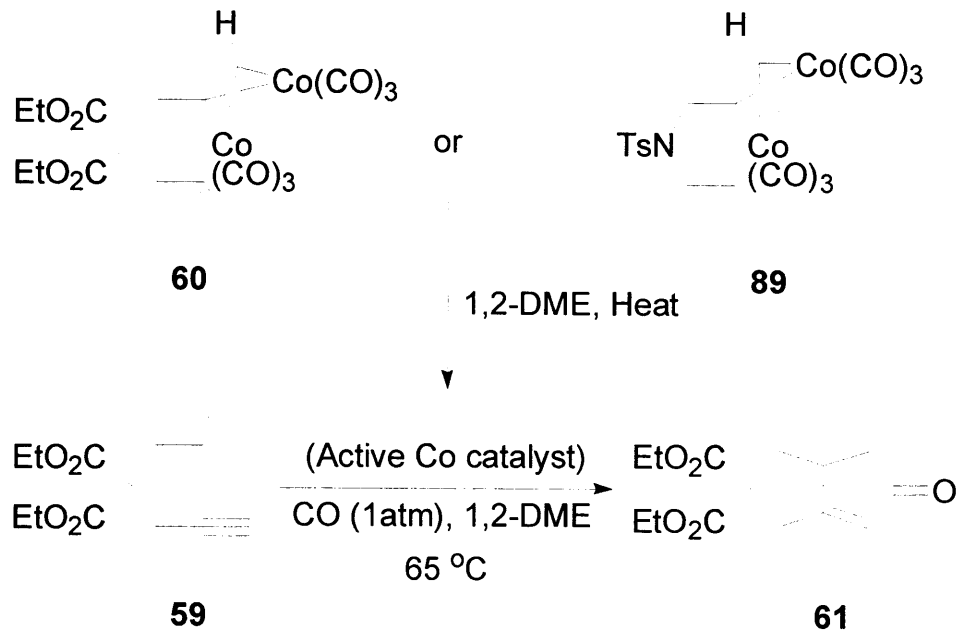
Several enynes, containing both terminal and internal alkynes as well as disubstituted alkenes, undergo the cyclisation in an efficient manner. Heteroatom containing enynes such as tosylamides also cyclised efficiently. Yields ranged from 77-95% and some examples are illustrated in **Table 11**.

Table 11. Thermally promoted PKRs catalysed by complex 185

Entry	Substrate	Product	Yield (%)[a]
1	 **186**	 **187**	86[b]
2	 **188**	 **189**	95[c]
3	 **190**	 **191**	90[d] (dr > 20:1)
4	 **146**	 **147**	92[d]

[a] All reactions were performed using substrate concentration of 0.1 M with 5 mol% Et_3SiH, 15 mol% $CyNH_2$. [b] 7.5 mol% alkyne-cobalt complex. [c] 5 mol% alkyne-cobalt complex at 65 °C. [d] 10 mol% alkyne-cobalt complex.

Krafft[57] has reported a modification of the above procedure in which the reduction step is not needed. They carried out the Pauson-Khand reaction of a dicobalt hexacarbonyl complex of an enyne under a carbon monoxide atmosphere which generated the appropriate catalyst thus making the reduction step unnecessary. Although it may not always be practical, one can envision using a catalytic amount of the dicobalthexacarbonyl complex of the actual substrate of interest. **Scheme 51** illustrates this concept.



Scheme 51

Table 12.Comparative PKR of enyne 59 catalysed by DCHC 60 or 89

Entry	Catalyst	Catalyst (%)	T (°C)	Time (h)	Yield (%)
1	$Co_2(CO)_8$	10	65	15	80
2	**60**	10	70	5	79
3	**89**	10	70	2	78

The yield of bicycle when the dicobalt hexacarbonyl complex of the substrate enyne **60** is used as the catalyst is 79% (entry 2), whereas the yield is 78% when the dicobalt hexacarbonyl complex of the nitrogen containing enyne **89** is used (entry 3). Another point worth noting is that the yield of the reaction when $Co_2(CO)_8$ is used is 80% (entry 1), hence these conditions do not improve the use of commercial dicobalt octacarbonyl. Advantages of this method over using commercial dicobalt octacarbonyl are (i) these complexes are air stable whereas dicobalt octacarbonyl is air sensitive and, (ii) reaction with dicobalt hexacarbonyl complexes goes to completion much faster than with dicobalt octacarbonyl, in most cases.

The range of substrates that undergo cyclisation under these conditions is the same as that reported by Livinghouse[56]. Yields of the reactions are also comparable. Again in the

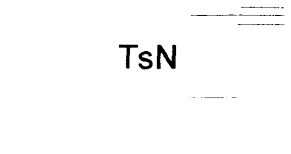
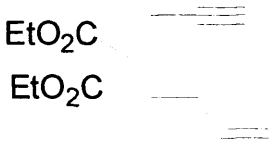
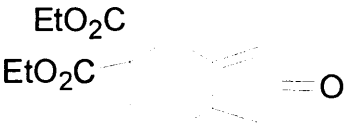
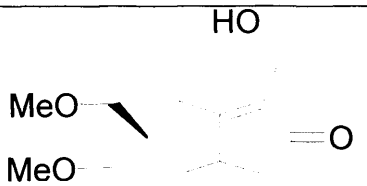
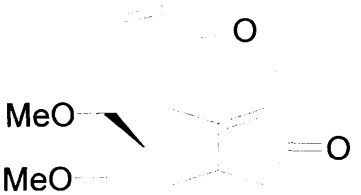
presence of cyclohexylamine, the reaction proceeded in higher yields in some cases, however the outcome of adding $CyNH_2$ is unpredictable.[57]

1.4.3 Photochemical catalytic Pauson-Khand reaction

Pagenkopf and Livinghouse[58] published a practical procedure for intramolecular photochemical catalytic Pauson-Khand reaction. They reported that high intensity visible light effectively promoted catalytic Pauson-Khand reaction at 50-55 °C and at 1 atmosphere of CO pressure. It was postulated that high intensity visible light might cause CO dissociation from the dicobalt hexacarbonyl complex of the enyne and therefore create a vacancy for the incoming alkene complexation. They stressed the importance of using high purity $Co_2(CO)_8$, the choice of an appropriate light source as well as reaction temperature in the range of 50-55 °C for successful catalytic reaction. Of the various solvents that were examined, 1,2-DME gave the best conversions.

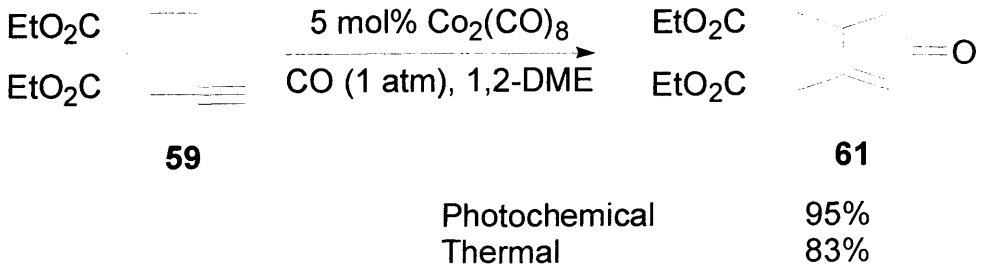
In general carbonylative cyclisation of enynes (0.1M in degassed 1,2-DME) could be effected by stirring in the presence of 5 mol% of $Co_2(CO)_8$ under 1 atm of CO pressure at 50-55 °C with "Q beam irradiation" for 12 hours. A 10^6 candlepower spotlight was also shown to be effective. Studies showed that tosylamides (**Table 13**, entry 1), terminal alkynes (**Table 13**, entry 2), free hydroxyl moieties (**Table 13**, entry 3), and ethers (**Table 13**, entry 4) were compatible with these reaction conditions. Yields obtained were between 67-95%.

Table 13. Catalytic Pauson-Khand Photocyclisations under 1 atm of CO

Entry	Substrate	Product	Yield (%)
1	 **192**	 **193**	90[a]
2	 **194**	 **195**	74
3	 **196**	 **197**	80
4	 **198**	 **199**	67[b]

[a] Ratio of diastereomers = 1.1:1.0. [b] 12.5 mol% $Co_2(CO)_8$ was used.

In a direct comparison between the thermal and photochemically promoted reactions, Livinghouse found the photochemically promoted catalytic Pauson-Khand reaction to be slightly more efficient as shown in **Scheme 52** for enyne **59**.

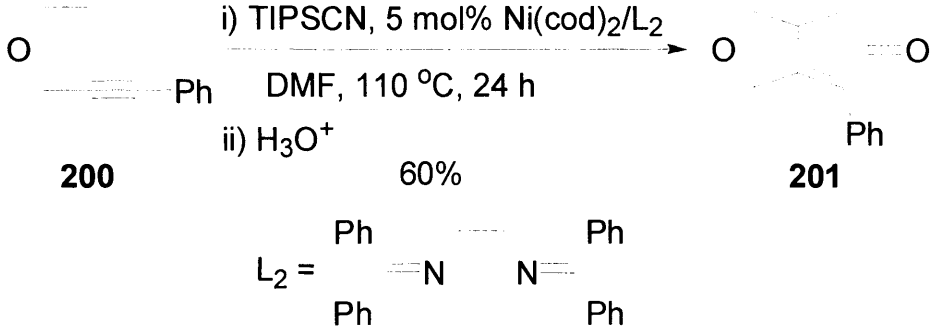


Scheme 52

1.4.4 Use of complexes of other metals

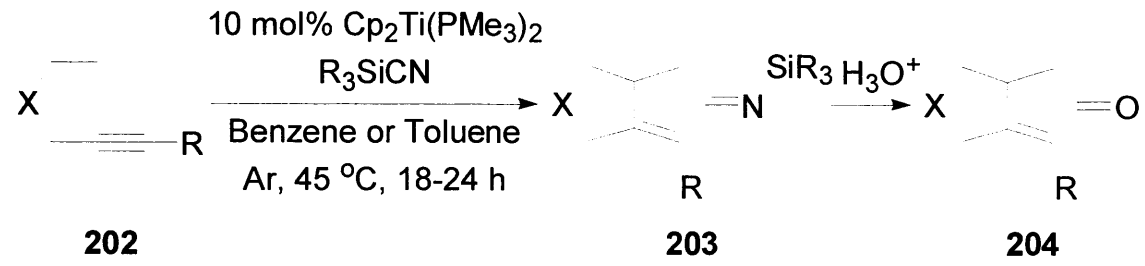
The use of alternative metals has been most effective in the development of a catalytic version of Pauson-Khand reaction and a brief overview follows.

Buchwald[59] has reported a catalytic transformation of enynes to iminocyclopentenes employing triisopropylsilyl cyanide and a Ni(0) complex generated *in situ* from $Ni(cod)_2$ and a bulky biketimine ligand. Acidic hydrolysis of iminocyclopentenes led to bicyclic enones. This method is tolerant of esters, ketones, nitriles, ethers and amines and an example is shown in **Scheme 53**.



Scheme 53

Buchwald[60] has also reported a catalytic Pauson-Khand reaction equivalent that utilises a titanocene as the catalytic species to promote cycloaddition between an enyne and an isocyanide. The resulting bicyclic iminocyclopentene is hydrolysed directly to the cyclopentenone. $Cp_2Ti(PMe_3)_2$ was used as an air and moisture stable inexpensive titanocene source. The combination of Cp_2TiCl_2 and 2 equivalents of EtMgBr (or *n*-BuLi) also functioned as *in situ*-generated titanocene equivalent. It was found that 10 mol% of $Cp_2Ti(PMe_3)_2$, under the conditions shown in **Scheme 54**, would convert enynes of type **202** and a slight excess of trialkylsilyl cyanide to the corresponding iminocyclopentene of type **203**. Mild hydrolysis then afforded bicyclic cyclopentenone of type **204**. Trialkylsilyl cyanides Me_3SiCN, $^tBuMe_2SiCN$ and Et_3SiCN all displayed similar activity.

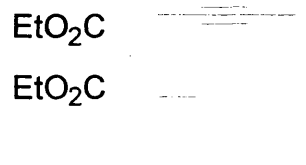
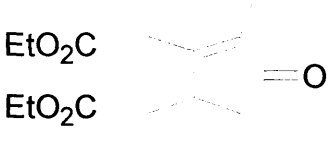
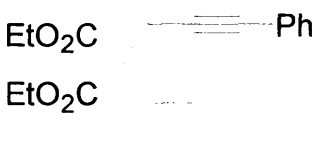
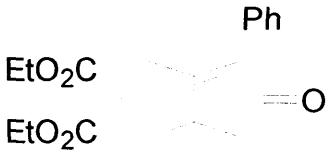
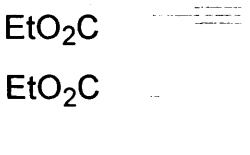
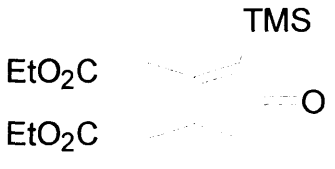
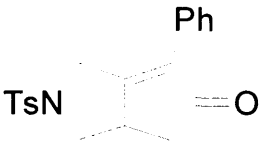


Scheme 54

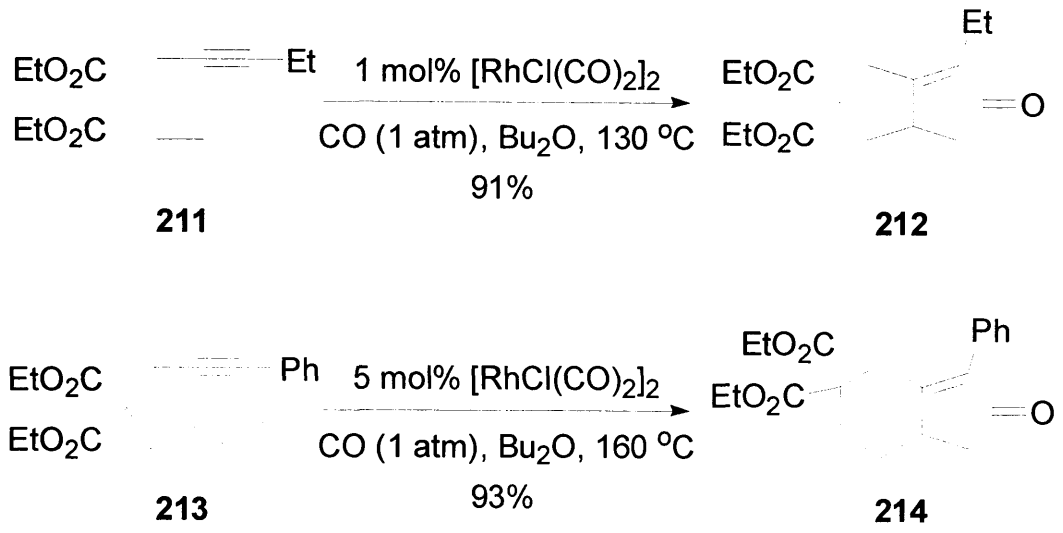
For sterically hindered enynes, more than 10 mol% of catalyst was required for complete conversion. This effect was postulated by the authors to be steric in nature as binding to the titanocene species is more difficult. The cyclisation reaction successfully forms both 5,5- and 5,6-fused ring compounds and tolerates the presence of ethers, nitrogen containing compounds and esters. Yields range from 42-80%.

Jeong and co-workers[61] developed the first rhodium(I) catalysed Pauson-Khand reaction. Of the various Rh catalysts tested, *trans*-[RhCl(CO)(dppp)]$_2$ gave the best results. A typical reaction protocol involved treatment of enyne with 2.5 mol% of catalyst in toluene at reflux for 24 h under 1 atm of CO. A few examples are illustrated in **Table 14**. Internal alkynes (entries 1 & 2) performed better than the terminal alkyne **59** (entry 3). While alkyl and aryl substituted alkynes **116** and **205** (entries 1 & 2 respectively) provided excellent chemical yields of products, trimethylsilyl-substituted alkyne **207** (entry 4) remained inert under the conditions described above. Oxygen and nitrogen containing enynes **200** and **209** (entries 5 & 6 respectively) also gave good yields in this reaction as shown in **Table 14**.

Table 14. *trans*-[RhCl(CO)(dppp)]$_2$ catalysed intramolecular PKRs

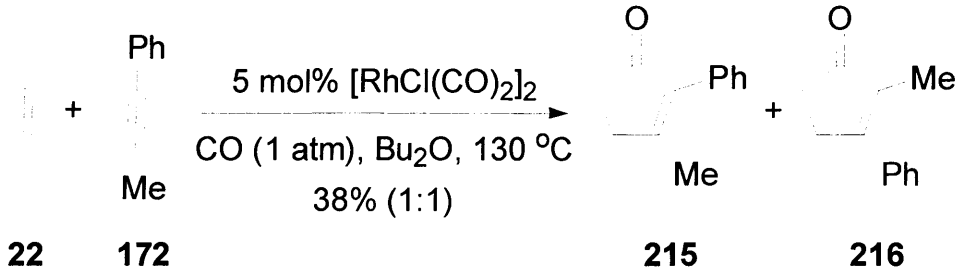
Entry	Substrate	Product	Yield (%)
1	 **116**	 **117**	96
2	 **205**	 **206**	99
3	 **59**	 **61**	55
4	 **207**	 **208**	0
5	 **200**	 **201**	82
6	 **209**	 **210**	97

Narasaka[62] has reported that [RhCl(CO)$_2$]$_2$ serves as a catalyst of the intra- and inter-molecular Pauson-Khand reaction. [RhCl(CO)$_2$]$_2$ served as a catalyst for the intramolecular cycloaddition reaction of 1,6- and 1,7-enynes which were converted to cyclopentenone under 1 atm of CO (**Scheme 55**).



Scheme 55

Intermolecular reaction of ethylene **22** with 1-phenylprop-1-yne **172** was also reported (**Scheme 56**).

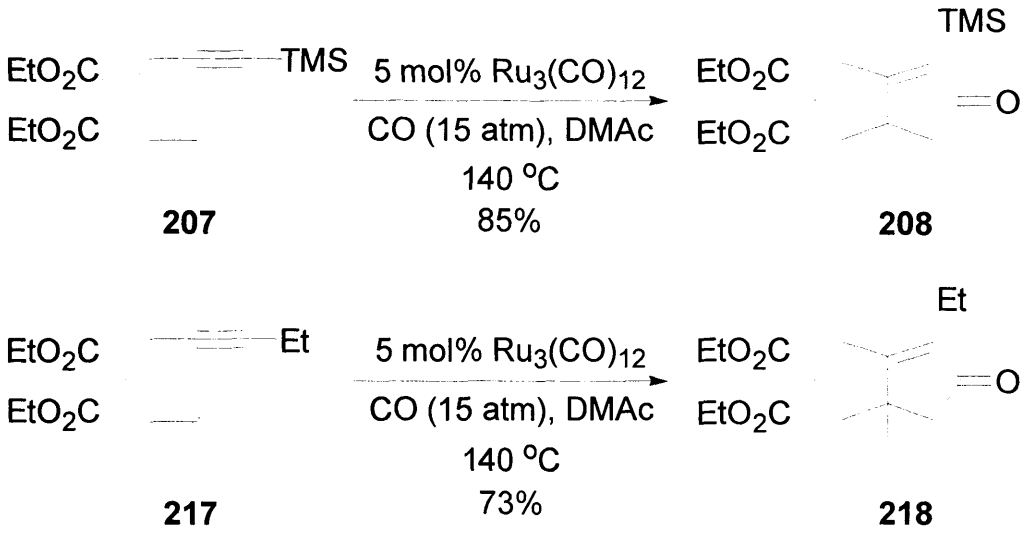


Scheme 56

Several advantages of using this catalyst were reported including the use of low CO pressure, using electron deficient alkenes as well as electron deficient alkynes in the enyne moiety.

Mitsudo[63] reported the first example of employing ruthenium in catalytic Pauson-Khand reaction. A typical procedure involves heating 5 mol% of $Ru_3(CO)_{12}$ and an enyne in *N,N*-dimethylacetamide at 140 °C under 15 atm of CO. Yields of reactions varied from 41%-89%. The reaction of enynes with an alkyl group either at the internal or external carbon of the olefinic moiety also proceeded to give the corresponding bicyclic cyclopentenones exclusively. Trimethylsilyl substituted enyne **207**, which gave the

desilylated product in the titanocene-catalysed reaction of enynes with silylcyanide, also gave the corresponding silylated product **208** in 85% yield as shown in **Scheme 57**.



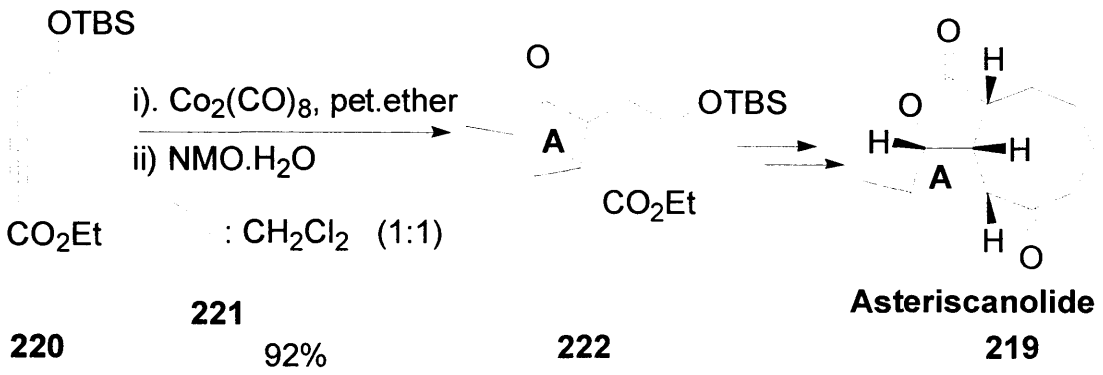
Scheme 57

1.5 Natural product synthesis using the Pauson-Khand reaction

There has been a dramatic increase in the use of the Pauson-Khand reaction for the synthesis of numerous natural products. The cyclopentane ring is quite common in nature and the Pauson-Khand adducts are easily functionalised. Hence this reaction has been employed in various syntheses of natural products. These include the synthesis of prostaglandins, different triquinanes and polyquinanes like ceratopicanol[64], kainic acid[65], hirsutene[66], epoxydictymine[67], xestobergsterol[68], spatane[69], dendrobin[70,71], hydroxymethylacylfulvene (HMAF)[72], nortaylorione[73] and β-cuparenone[74].

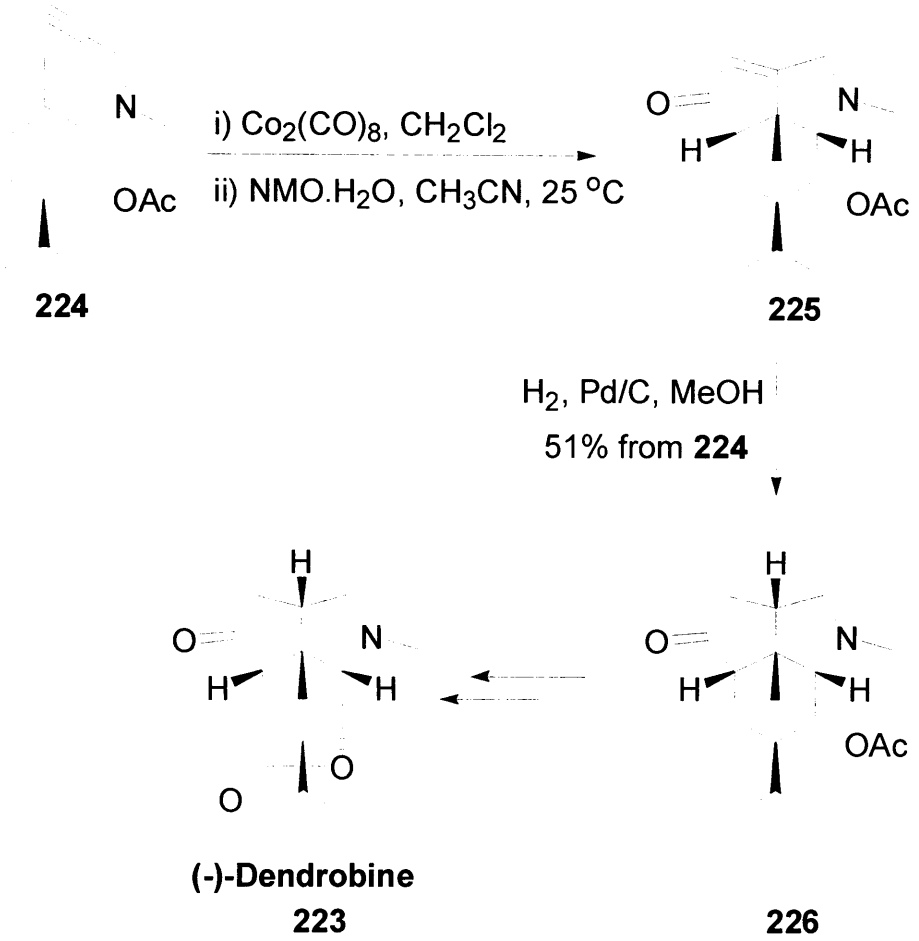
Some recent examples are briefly discussed below.

Krafft[75] has reported the total synthesis of a sesquiterpene, asteriscanolide **219**. The synthesis is based on a regioselective Pauson-Khand reaction of **220** with propene **221** (**Scheme 58**). The formation of the cyclooctane ring is achieved in the final stages by means of a ring closing metathesis reaction.



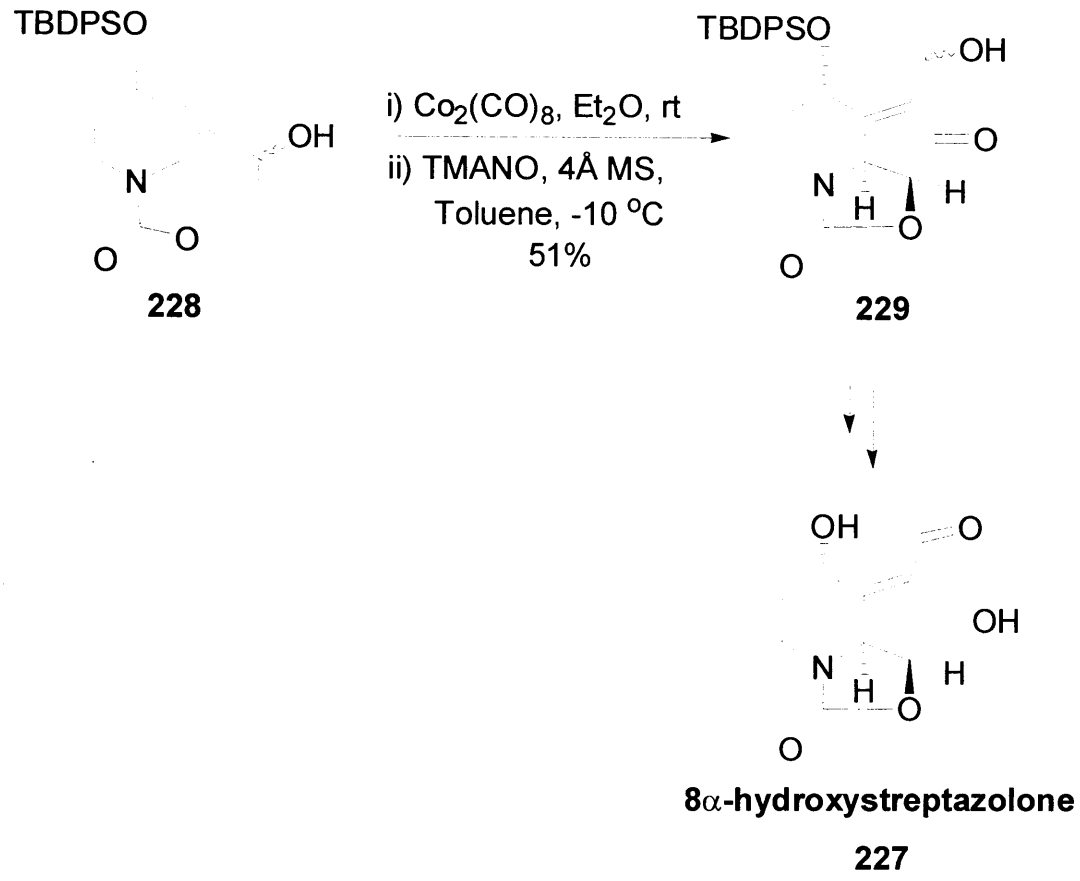
Scheme 58

The intramolecular variant of the Pauson-Khand cycloaddition has been particularly useful in the rapid synthesis of complex fused tricycles such as dendrobine. (-)-Dendrobine **223** is an alkaloid that exhibits antipyretic and hypotensive activity and has attracted much attention as a synthetic target. Cassayre and Zard[70,71] completed an asymmetric synthesis of (-)-dendrobine, setting the stereochemical features of the tricycle with the Pauson-Khand cycloaddition of enyne **224**. This step is shown in **Scheme 59**.



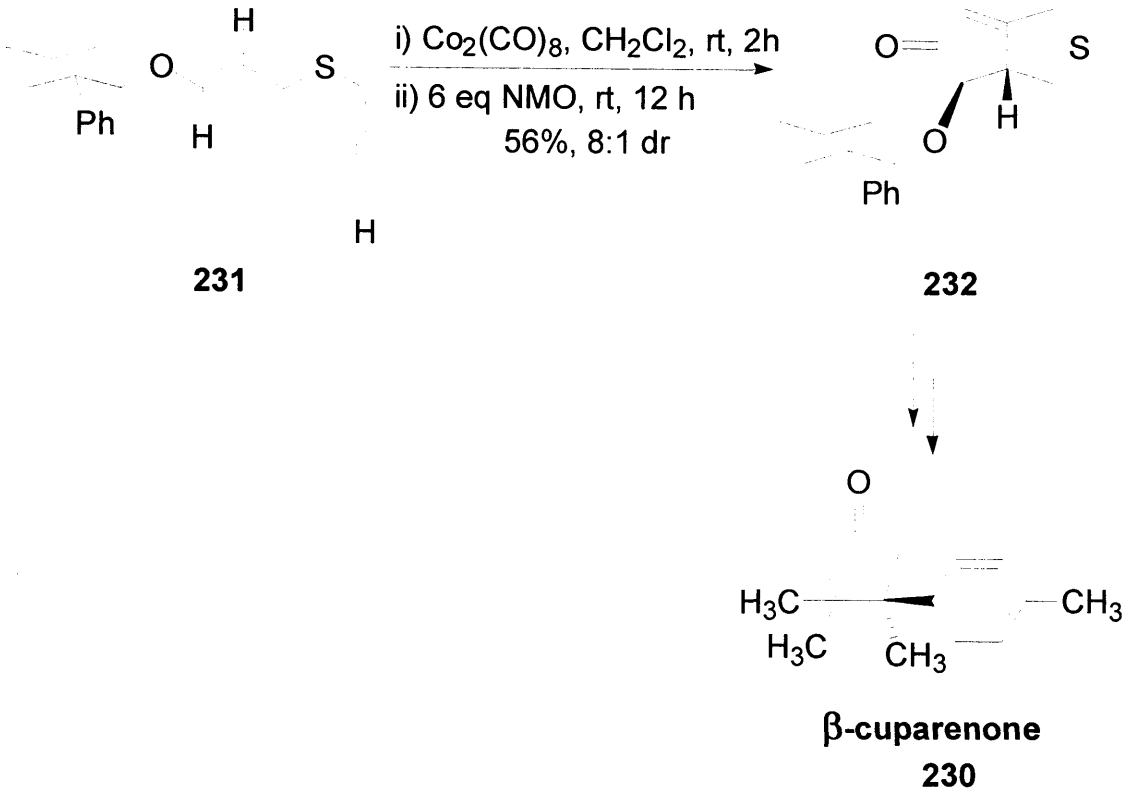
Scheme 59

Mukai[76] has effected a total synthesis of 8α-hydroxystreptazolone **227** in which the key step is an intramolecular Pauson-Khand reaction carried out on a 2-oxazolone derivative **228** (**Scheme 60**). This implies the use of an enamine as the olefinic part of the reaction. The Pauson-Khand reaction is accomplished in a highly stereoselective manner in 51% yield as shown in **Scheme 60**. This compound is a natural product possessing antifungal and antibiotic properties.



Scheme 60

Synthesis of monocyclic cyclopentenones can suffer from lack of regioselectivity. In their 1996 synthesis of monocyclic β-cuparenone **230**, Moyano and Pericas[74] avoided this problem by use of a removable sulfur tether to transform the reaction to the more predictable intramolecular variant. By utilisation of a chiral auxiliary, they were able to effect the transformation asymmetrically in 56% yield (**Scheme 61**). Removal of the chiral auxiliary and reductive cleavage of the sulfide afforded the desired monocyclic product.



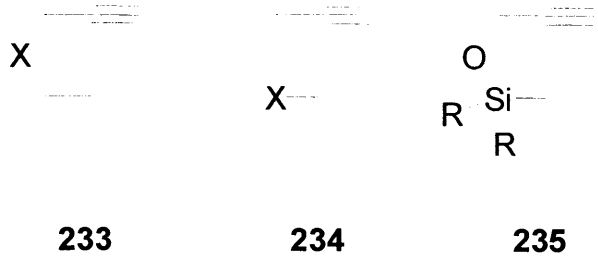
Scheme 61

1.6 Aims of the project

1.6.1 Silicon-tethered enynes

Numerous intramolecular Pauson-Khand reactions are known in which the chain linking the alkene and alkyne partners contains a heteroatom.[1] In almost all of these examples, the heteroatom (O, N or S) is in the 4-position (**233** in **Figure 4**). A novel and potentially interesting modification would thus be investigation of substrates with a heteroatom linked directly to the alkene (**234** in **Figure 4**).

The ease of formation and cleavage of silicon-oxygen and silicon-carbon bonds suggested that vinyl silyl ethers (**235** in **Figure 4**) would be readily synthesised and that their Pauson-Khand reaction would yield bicyclic products. It was hoped that further transformations of these Pauson-Khand adducts would lead to a wide range of structures.



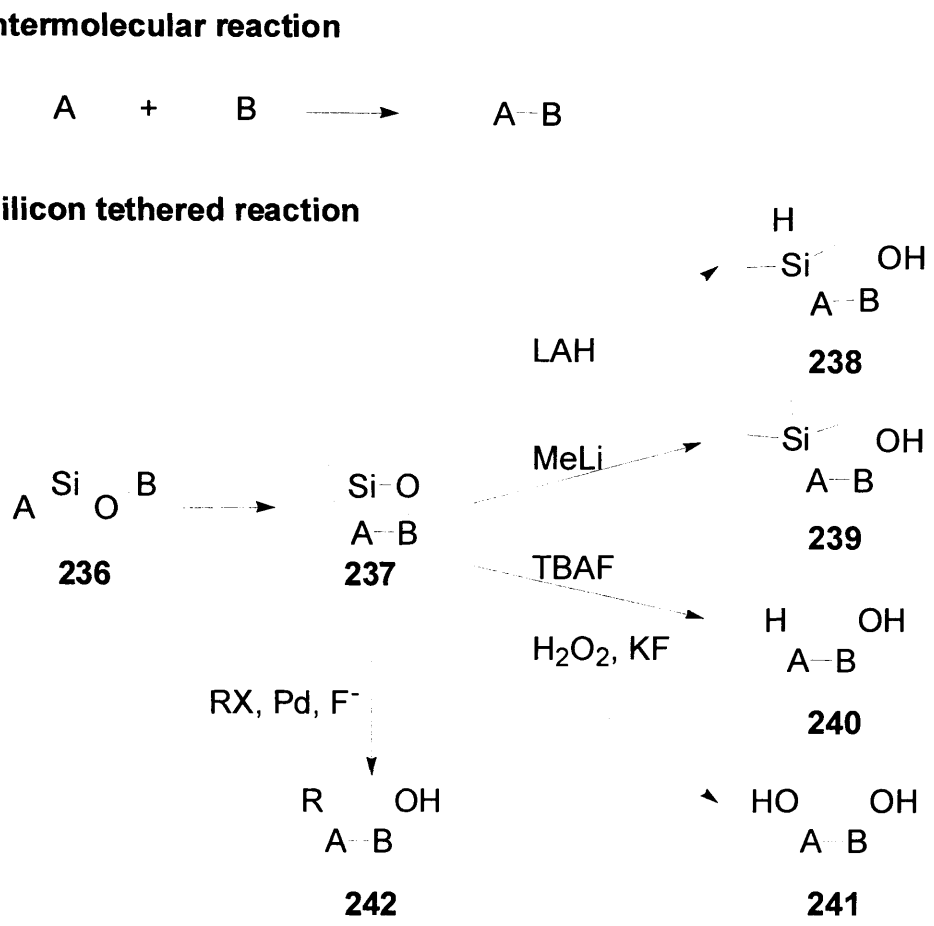
233 **234** **235**

Figure 4

The initial aim of the project was to fully explore the scope of silicon-tethered Pauson-Khand reactions and various transformations of the cyclopentenone products.

1.6.1.1 Advantages of using silicon-tethered reactions

An important goal in modern organic synthesis is the development of reliable stereoselective, preferably enantioselective chemical reactions. Intramolecular reactions possess a high degree of stereoselectivity which the corresponding intermolecular versions often do not possess. A temporary silicon connection, usually ether, can transform an intermolecular reaction into an intramolecular one, by transiently connecting both partners through a silicon linkage such as in **236** (**Scheme 62**). This temporary connection endows the reaction with entropic advantages, by bringing the reacting ends of the molecule closer, as well as regiospecificity and often stereoselectivity.[77]

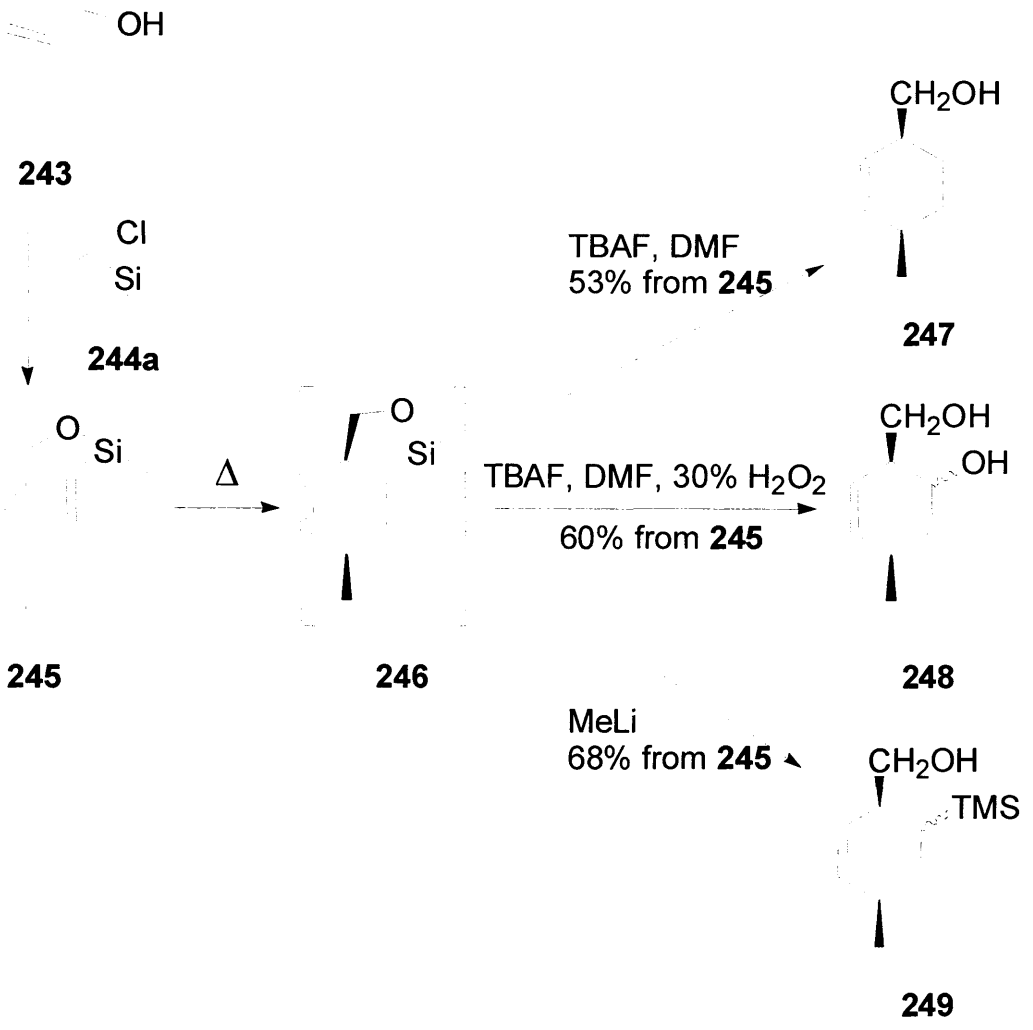


Scheme 62

The choice of silicon group as a tether is mainly attributed to the ease of formation of silicon derivatives as well as their inert behaviour under most reaction conditions.[78] The crucial silicon link of **236** is generally created by a simple silylation of a hydroxy group by a commercially available chlorosilane. Another incentive for using a silicon tether is the variety of products that can be obtained by further reaction of silacycle **237** as shown in **Scheme 62**. Silacycle **237** can be reduced using lithium aluminium hydride (LAH) to obtain a hydrosilane **238**. Organometallic reagents like methyllithium will cleave the silacycle **237** to provide the trimethylsilyl alcohol **239**. Tetra-*n*-butylammonium fluoride (TBAF) would reductively cleave the silacycle **237** and lead to the alcohol **240**. Oxidative cleavage of silicon-carbon bond of silacycle **237**, using Tamao oxidation conditions, would deliver diol **241** with retention of configuration. Palladium catalysed coupling of organosilanes with allyl, alkenyl and aryl halides and triflates has led to their use in carbon-carbon bond formation, as in the transformation of **237** to **242** (**Scheme 62**).[77]

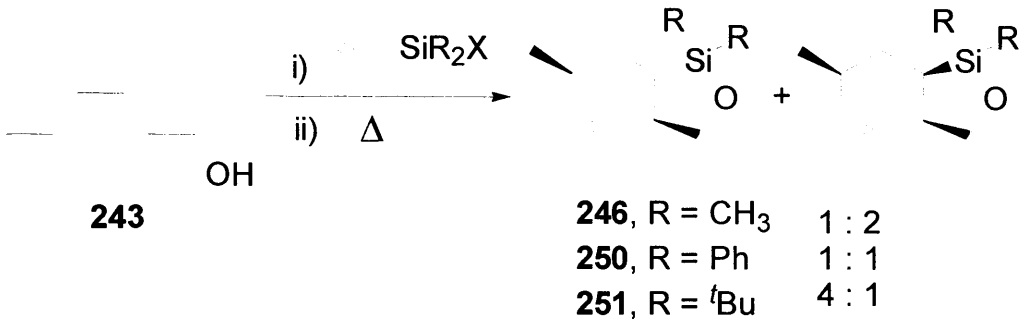
Use of a silicon tether has been applied to many different types of reaction including radical cyclisations, cycloadditions and nucleophilic additions.[77] Use of a silicon tether in Diels-Alder reactions has been extensive. In contrast to the bimolecular case, intramolecular Diels-Alder reactions have the advantage of lower activation entropy because the two reacting components are already in proximity, resulting in favourable kinetics.

Stork[79] and Sieburth[80] have reported intramolecular Diels-Alder reactions of vinylsilanes by simply connecting dienols to vinylchlorosilanes. Thus the thermolysis (160-190 °C) of **245** results in the formation of silafuran **246**, which can be transformed into alcohol **247**, diol **248** or trimethylsilyl alcohol **249**, in good overall yield as shown in **Scheme 63**. It is noteworthy that the overall formation of alcohol **247** from sorbyl alcohol **243** is equivalent to the use of ethylene as a dienophile, and that the steps in **Scheme 63** can be consolidated into a single operation.



Scheme 63

The disposable silyl substituent can influence the stereochemical outcome of this reaction. With the diene **243**, a dimethylsilyl group yielded a 1:2 ratio of products in which the *cis* isomer was the major product (**Scheme 64**). Changing to a diphenylsilyl group gave a 1:1 ratio of products and the di-*tert*-butylsilyl group resulted in a *trans*/*cis* ratio of 4:1. Steric bulk around the silicon moiety thus tended to favour the *trans* product (**Scheme 64**).[77]

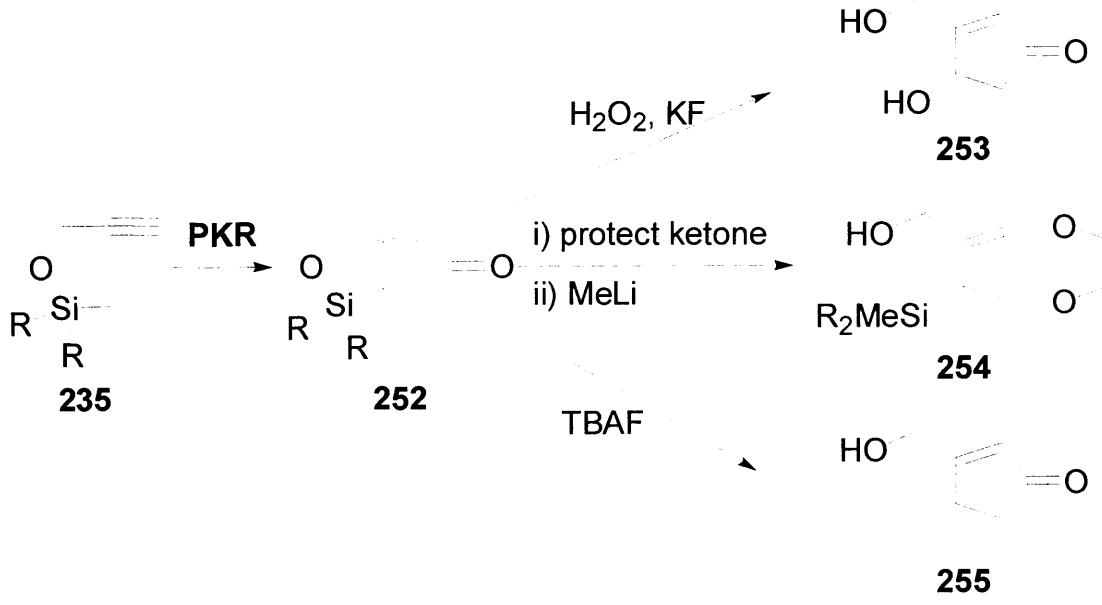


Scheme 64

These examples illustrate the various ways in which silicon tether can help control reactivity, regioselectivity and often stereoselectivity of various reactions.

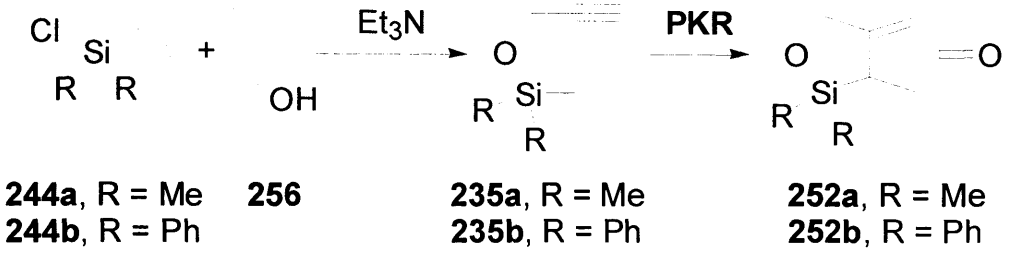
1.6.1.2 Silicon tethered enynes as substrates for PKR

The initial goal of our research was to investigate the Pauson-Khand cyclisation of vinylsilyl enynes of the type **235** (**Scheme 65**). The cyclised silyl ether **252** may be converted to a diol **253** by Tamao oxidation[81], to an allylsilane **254** by ketone protection and addition of methyllithium, or to a desilylated alcohol **255**,[79] formally a product of a Pauson-Khand reaction with ethylene (**Scheme 65**).



Scheme 65

It was hoped that enynes **235a** and **235b** in **Scheme 66** would be synthesised from silylation of propargyl alcohol **256** with commercially available silyl chlorides **244a** and **244b**. With these enynes in hand, formation of bicycles **252a** and **252b** would be optimised using various Pauson-Khand conditions. Further transformations of these bicycles would then be investigated as shown in **Scheme 65** above.

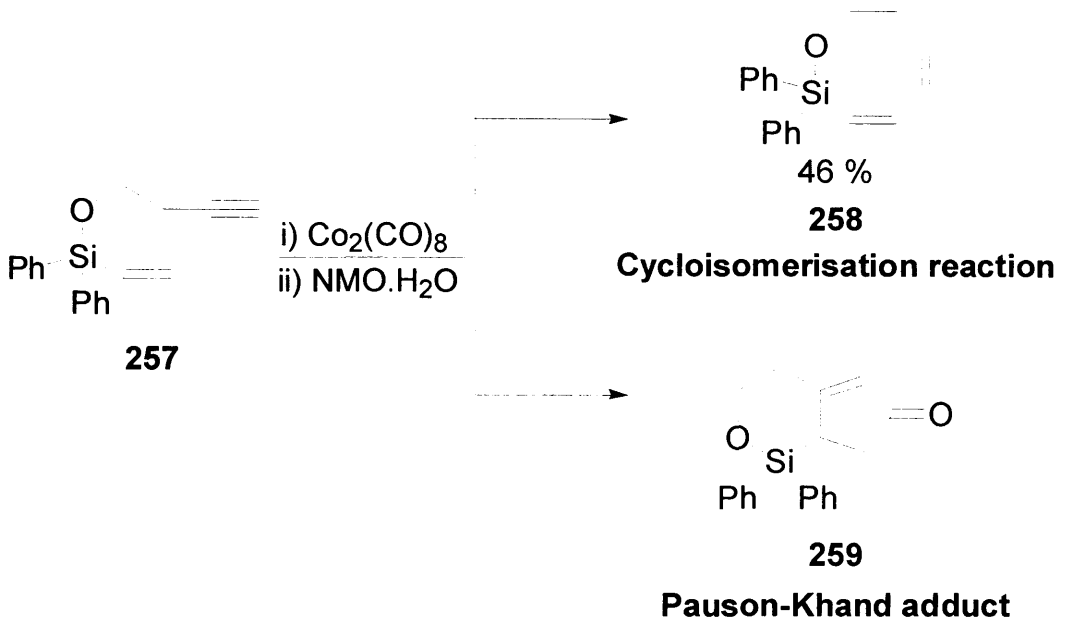


Scheme 66

Once optimum conditions for the Pauson-Khand cycloaddition have been found, variations in the substrates **235a** and **235b** would lead to conclusions about the scope and limitations of vinylsilyl enynes as substrates for Pauson-Khand reaction.

1.6.1.3 Precedent for using silicon tethered substrates in PKR

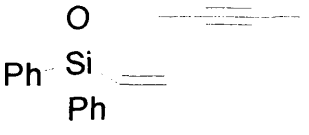
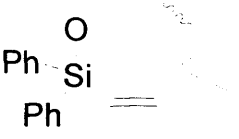
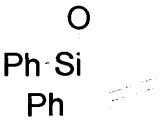
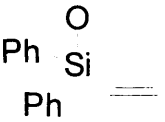
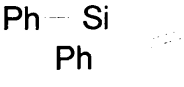
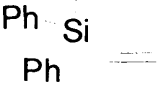
At the start of this project, there was only one report of using silicon tethered enynes as substrates in Pauson-Khand reaction, by Saigo and coworkers[82]. They reported that attempted *N*-oxide promoted Pauson-Khand reaction of 3-sila-1,7-enynes led to a new cycloisomerisation reaction to give eight-membered cyclic dienylsilanes instead of bicyclic Pauson-Khand cycloadducts. During their initial studies on enyne **257**, unexpected formation of dienylsilane **258** occurred instead of cyclopentenone derivative **259** (**Scheme 67**). Saigo has argued that this reaction, although unexpected at the time, is useful for the construction of eight-membered rings which are common in both natural and unnatural compounds.



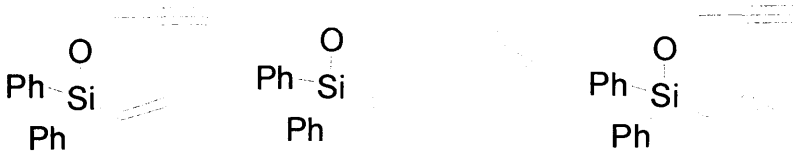
Scheme 67

Several examples demonstrate the generality and utility of the vinylsilane cycloisomerisation reaction, as illustrated in **Table 15**. Presence of a methyl substituent at the alkyne terminus is tolerated (entry 1) whereas a TMS substituent retarded the cycloisomerisation process. 1,7-Enynes that have a methyl substituent at the alkenyl moiety, (entry 2), also underwent cycloisomerisation. The enyne **264**, where oxygen is replaced with a carbon (entry 3), also yielded cyclooctadiene **265**.

Table 15. Cycloisomerisation reaction of 1,7-enynes

Entry	Substrate	Product	Yield (%)
1	 **260**	 E/Z = 3:2 **261**	30
2	 **262**	 **263**	24
3	 **264**	 **265**	22

Neither the homologous 1,6-enyne (**235b** in **Figure 5**) nor 1,8-enyne (**266** in **Figure 5**) underwent cycloisomerisation. In the reaction of allyl(propargyloxy)silane (**267** in **Figure 5**), no cycloisomerised product was detected. In this case only decomposition of starting material occurred. This shows that this cycloisomerisation reaction is peculiar to 3-sila-1,7-enynes.

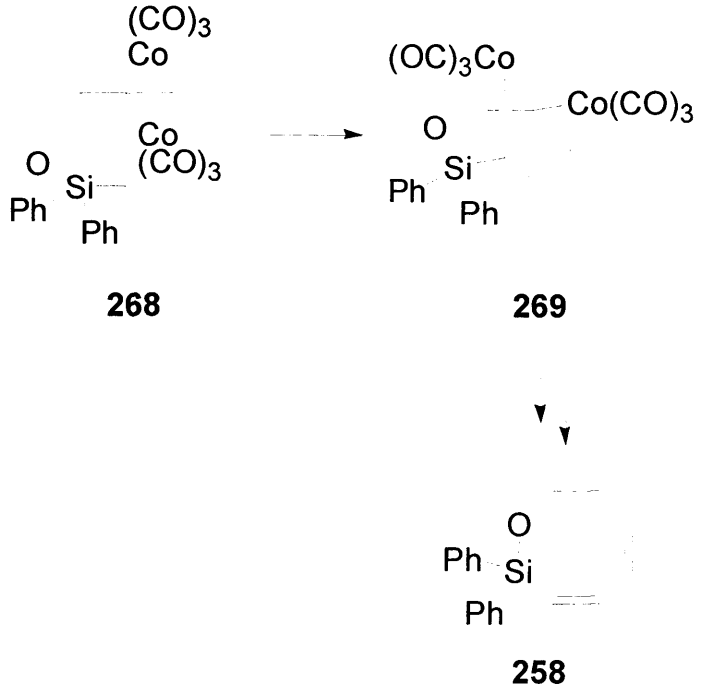


235b **266** **267**

Figure 5

Both the mechanism of this transformation as well as the reasons for the mechanistic divergence are unclear. A possible explanation by Saigo involves the insertion of alkene into the distal C-Co bond, rather than proximal bond, leading to a key intermediate **269**

that can be converted to the observed product by successive β-hydride abstraction, reductive elimination and decomplexation (**Scheme 68**).



268 **269** **258**

Scheme 68

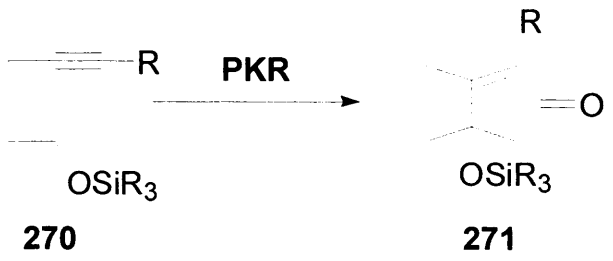
Substitution of carbons in the tether with heteroatoms such as nitrogen[83, 84] and oxygen[26] leads to the expected Pauson-Khand cycloadducts.

During the course of our research, Pagenkopf[85,86] reported the use of vinylsilane derived enynes and Brummond[87] reported the use of silicon tethered allenes as substrates for Pauson-Khand reaction respectively. Their work will be discussed in chapter 2.

1.6.2 Silyl enol ethers as substrates in PKR

As the project developed, we decided to investigate silyl enol ethers of type **270** (**Scheme 69**) as substrates for the Pauson-Khand reaction.

There are a few examples in the literature where alkyl enol ethers have been used in Pauson-Khand reaction[66,88], however silyl enol ethers of type **270** have not been investigated as substrates for intramolecular Pauson-Khand reaction.



Scheme 69

Pauson-Khand reaction of silyl enol ethers would lead to bicyclic cyclopentenones with β-OH functionality in the resulting cyclopentenone ring, after the removal of the silyl group. This would be useful for further manipulation of the bicycle and may prove useful in the synthesis of several natural products.

Initially, we decided to synthesise two substrates, **272a** and **272b**, to find the optimum reaction conditions for cyclisation.

272a, R = H
272b, R = CH_3

Figure 6

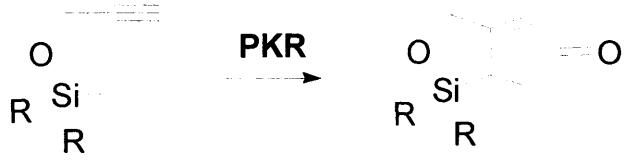
We then hoped to synthesise substrates with varying substituents on both the alkene and the alkyne moiety to define the scope and limitations of using silyl enol ethers as substrates for Pauson-Khand reaction.

2. Results and Discussion

2.1 Vinylsilane-derived enynes as substrates for the Pauson-Khand reaction

2.1.1 Synthesis of Substrates

The initial goal of the research was to investigate the Pauson-Khand cyclisation of silicon tethered enynes **235a** and **235b** (**Scheme 70**).

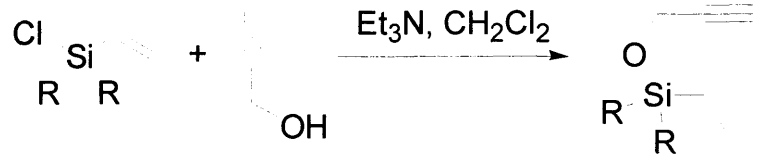


235a, R = Me
235b, R = Ph

252a, R = Me
252b, R = Ph

Scheme 70

Enynes **235a** and **235b** were synthesised from the commercially available starting materials propargyl alcohol **256** and chlorosilanes, chlorodimethylvinylsilane **244a** and chlorodiphenylvinylsilane **244b** using a literature procedure[80] as shown in **Scheme 71**. The synthesis of dimethyl enyne **235a** proceeded in low yield (8%), due to its volatility.



244a, R = Me
244b, R = Ph

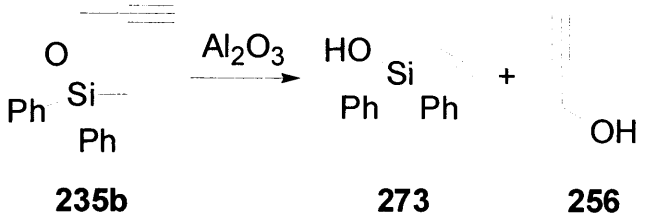
256

235a, R = Me
235b, R = Ph

Scheme 71

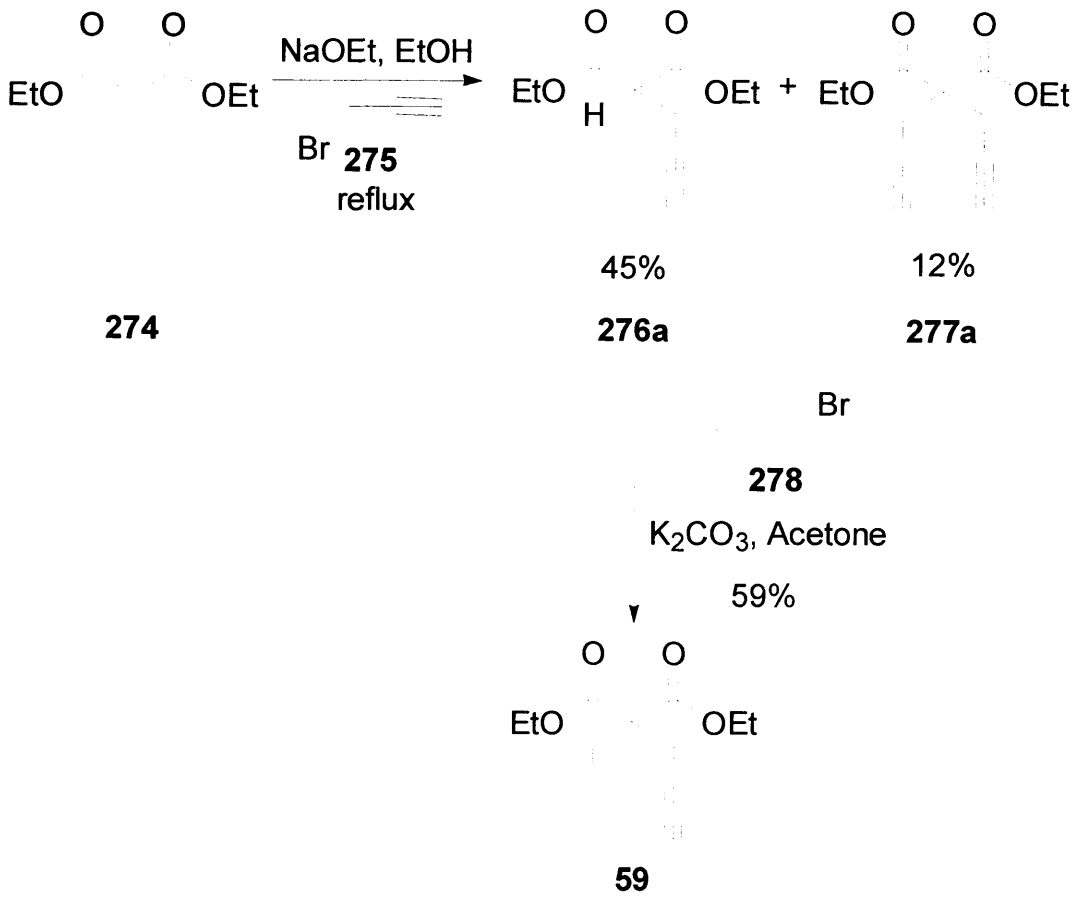
The synthesis of diphenyl enyne **235b** proceeded with ease. The purification of this enyne by flash column chromatography using silica led to complete decomposition. Use of deactivated grade III alumina as solid support led to decomposition of the enyne **235b** into diphenylvinylsilanol **273**, which was characterised, and presumably propargyl

alcohol **256** (**Scheme 72**). Enyne **235b** could however be purified by flash column chromatography on Florisil®, which is neutral, and led to 73% yield. We selected enyne **235b**, for our preliminary cyclisation studies. It was used crude.



Scheme 72

We decided to synthesise a literature substrate, diethyl allylpropargylmalonate **59**, known to undergo Pauson-Khand cyclisation reaction along with our silicon tethered enyne **235b,** so that the reactivities of both substrates could be compared under the same cyclisation conditions. Enyne **59** was synthesised using literature procedures[89,90] and is illustrated in **Scheme 73**. Commercially available diethyl malonate **274** was deprotonated with sodium ethoxide and then propargylated using propargyl bromide **275** yielding diethyl propargylmalonate **276a** in 45% yield.[89] A side product of the reaction was diethyl dipropargylmalonate **277a** which was isolated as a white crystalline solid in 12% yield. Allylation of diethyl propargylmalonate **276a** using potassium carbonate as base and allylbromide **278** as the alkylating agent yielded the desired enyne **59** in 59% yield.[90]

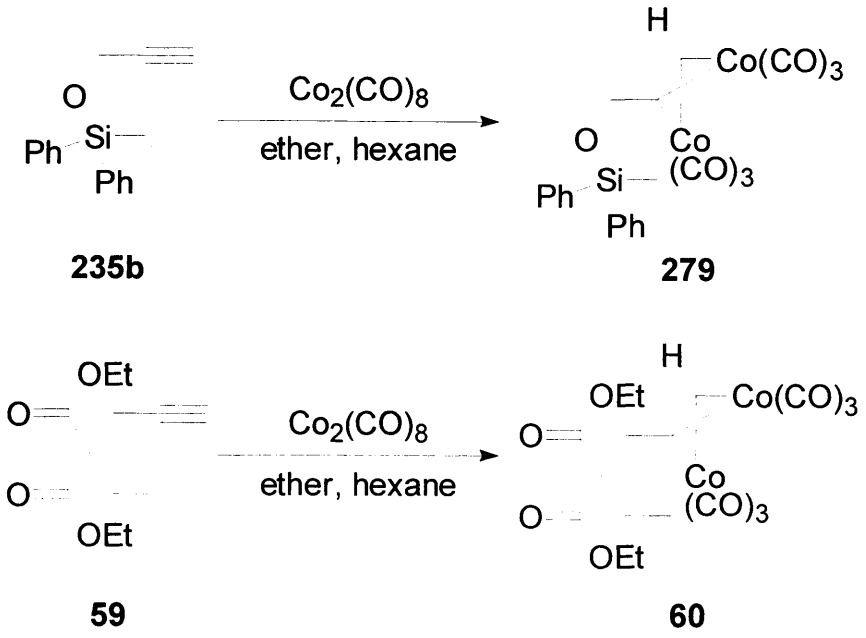


Scheme 73

2.1.2 Pauson-Khand reactions of silicon-tethered enyne 235b and malonate-derived enyne 59

Initially we decided to synthesise and isolate dicobalt hexacarbonyl complexes **279** from **235b** and **60** from **59** (**Scheme 74**). It was hoped that isolation of these complexes would lead to rapid studies on the PKR of these two substrates under various conditions, and hence lead to optimisation of reaction conditions. Once the optimum conditions were found, we hoped to synthesise a series of substrates to analyse the scope and limitations of the Pauson-Khand reaction of silicon-tethered enynes.

Dicobalt hexacarbonyl complexes **279** and **60** were synthesised by stirring the substrate with approximately 1.2 equivalents of dicobalt octacarbonyl in a hydrocarbon or ethereal solvent at room temperature for 1.5 hours under nitrogen atmosphere as shown in **Scheme 74**.

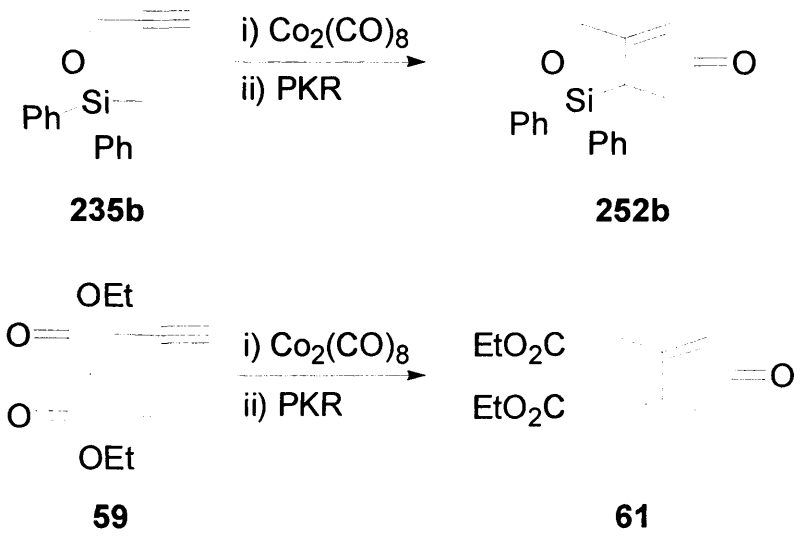


Scheme 74

Purification of the dicobalt hexacarbonyl complex **279** of silicon-tethered enyne **235b** by flash column chromatography proved to be very difficult as the signals in the ^{1}H NMR spectrum were very broad, presumably due to the presence of paramagnetic cobalt species, and hence were very difficult to interpret. The dicobalt hexacarbonyl complex **279** was isolated only once by flash column chromatography using silica as solid support. Hexane was first used to remove inorganic cobalt impurities and then solvent of increasing polarity (1-50% ether in hexane) was used to obtain the desired complex **279** in 46% yield. Although the signals in the ^{1}H NMR spectrum were still broad, it showed that the terminal alkyne H in the complex **279** shifted downfield to 5.89 ppm from 2.39 ppm in the starting enyne **235b**. However this desired complex **279** proved to be thermally unstable. The deep red oil decomposed to a black solid on rotary evaporator at *ca.* 40 °C.

Due to the above mentioned difficulties in the isolation of complex **279**, we decided to synthesise it *in situ*, by stirring enyne **235b** and dicobalt octacarbonyl in a suitable solvent at room temperature under nitrogen. The crude complex was then subjected to Pauson-Khand cycloaddition conditions.

The dicobalt hexacarbonyl complex **60** of literature substrate **59** was also synthesised *in situ* and subjected to Pauson-Khand reaction without further purification. The PKR of substrates **235b** and **59** was expected to yield Pauson-Khand adducts **252b** and **61** respectively (**Scheme 75**).



Scheme 75

The results of Pauson-Khand studies for both the substrates **235b** and **59** are shown in **Table 16**.

Table 16. Pauson-Khand reactions of enynes 235b and 59

Entry	Conditions	Yield (%) **252b**	Yield (%) **61**
1	Toluene, reflux, N_2	0	30
2	Toluene, reflux, CO[a,b]	0	20
3	CH_3CN, 75 °C, N_2	0	44
4	CH_3CN, 75 °C, CO[a,b]	0	25
5	Degassed Hexane, 70 °C, CO[a,b]	0	58
6	1 : 3 (v/v) 1,4-dioxane, 2M NH_4OH, 100 °C	0	31
7	NMO, CH_2Cl_2, rt, N_2	0	25
8	*n*BuSMe, 1,2-DCE, 83 °C	0	34
9	SiO_2, 50 °C, Air	0	55

[a] $Co_2(CO)_8$ weighed under N_2 in a glove bag. [b] Pressure tube.

The crude dicobalt hexacarbonyl complexes **235b** and **60** were subjected, in parallel, to various different literature conditions for Pauson-Khand reactions. This included both thermal promotion of the reaction as well as use of various promoters.

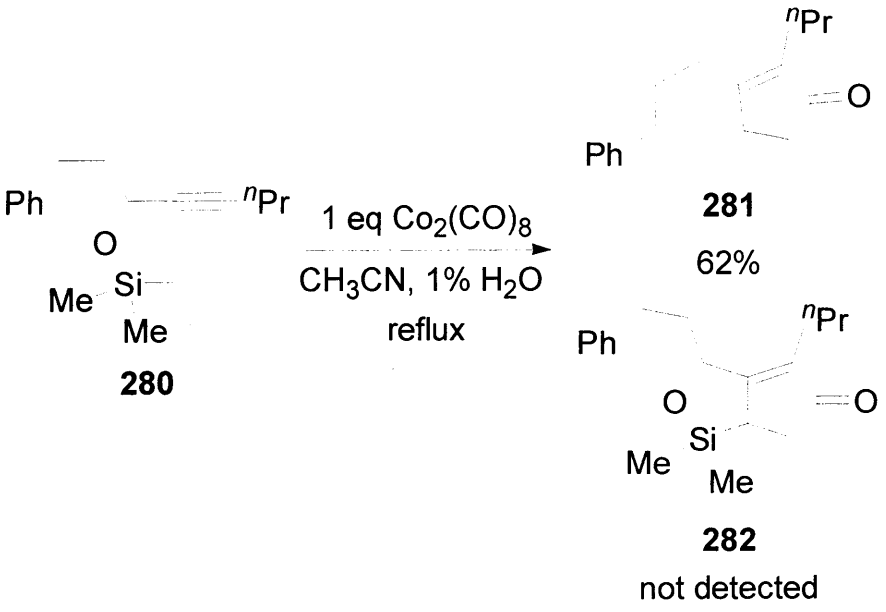
Reasonable yields of the bicycle **61** were obtained from literature substrate **59**, however the silicon-tethered substrate **235b** did not yield any of the desired cyclopentenone **252b** under all the conditions tested (**Table 16**). Due to the presence of paramagnetic cobalt impurities in the crude reaction mixtures, peaks in the ^{1}H NMR spectra were very broad and could not be interpreted. Hence it was necessary to carry out flash column chromatography on crude reaction mixtures to remove these impurities before obtaining any spectroscopic data. The mass recovery was very poor and samples were not clean enough to draw concrete conclusions about the course of the reactions. However cleavage of Si-O bond appeared to be occurring with loss of the silicon tether. Due to the inability to obtain ^{1}H NMR spectra of the crude reaction mixtures, it was impossible to say whether the Pauson-Khand reaction was not taking place in the first instance and/or the starting material was decomposing during the course of the reaction. Formation of the product and its decomposition upon purification by flash column chromatography was another possibility.

As can be seen from **Table 16** several literature conditions including thermal promotion (entries 1 & 3[91]) as well as use of promoters such as amines[28] (entry 6) *N*-methylmorpholine oxide[25] (entry 7) and *n*-butyl methyl sulfide[29] (entry 8) were investigated, however none of the conditions tested yielded any desired product. Flash chromatography of the crude reaction mixtures, using silica, alumina as well as Florisil®, did not lead to any conclusions about the course of these reactions as mixtures of unidentifiable products were obtained. However in some cases cleavage of silicon tether appeared to be occurring. Use of anhydrous conditions, (as dicobalt octacarbonyl is air and moisture sensitive) where dicobalt octacarbonyl was weighed under N_2 in a glove bag (entries 2, 3 & 4), use of CO pressure in a pressure tube (entries 2, 4 & 5) and use of degassed hexane (entry 5) also did not lead to isolation of the desired bicycle.

2.1.3 Pagenkopf's results

At this stage of our research, Pagenkopf[85,86] published work on the Pauson-Khand reaction of vinylsilane derived enynes. Their results showed that carbons bound to the silicon tether were reduced during the course of this reaction.[85]

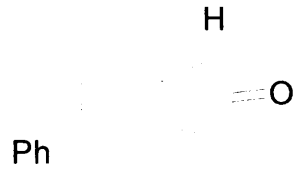
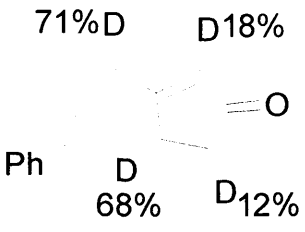
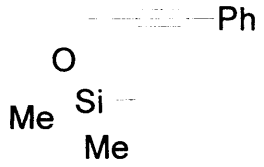
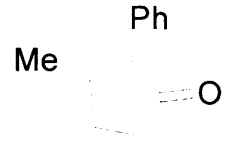
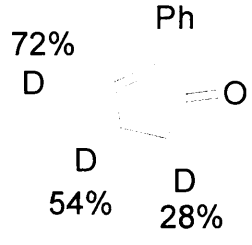
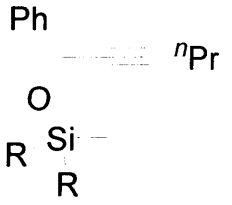
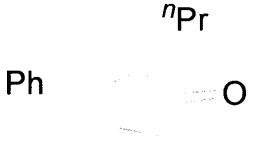
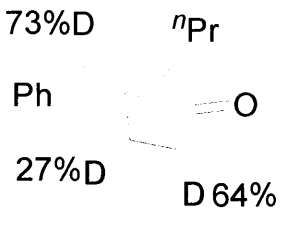
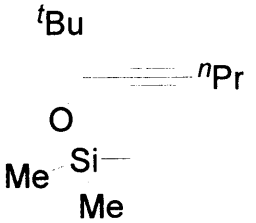
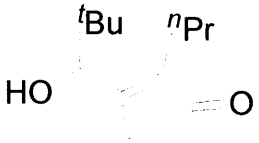
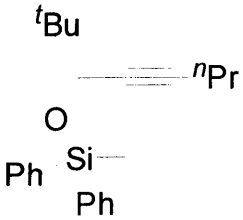
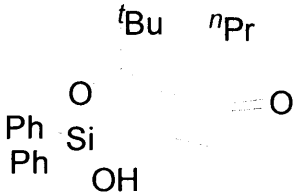
In the initial experiments to identify the optimum conditions for their model substrate **280**, several variants of Pauson-Khand reaction were tried. None led to the desired cyclopentenone **282**, but instead metal decomplexation, hydrolysis of the silyl ether and/or decomposition occurred[85]. However in refluxing acetonitrile containing 1% H_2O the dicobalt hexacarbonyl complex of **280** was converted to enone **281** in 62% yield (**Scheme 76**). The use of anhydrous acetonitrile (conditions we had tried) had a deleterious effect on the efficiency of the reaction and led to lowering the yields reported in **Table 17** by 30-65%.



Scheme 76

A variety of substrates with varying substituents in alkynyl and propargylic positions were subjected to the above mentioned conditions to test the generality of this new reaction. Some of the results are shown in **Table 17**.

Table 17. Pagenkopf's PKR of vinylsilane-derived enynes[85,86]

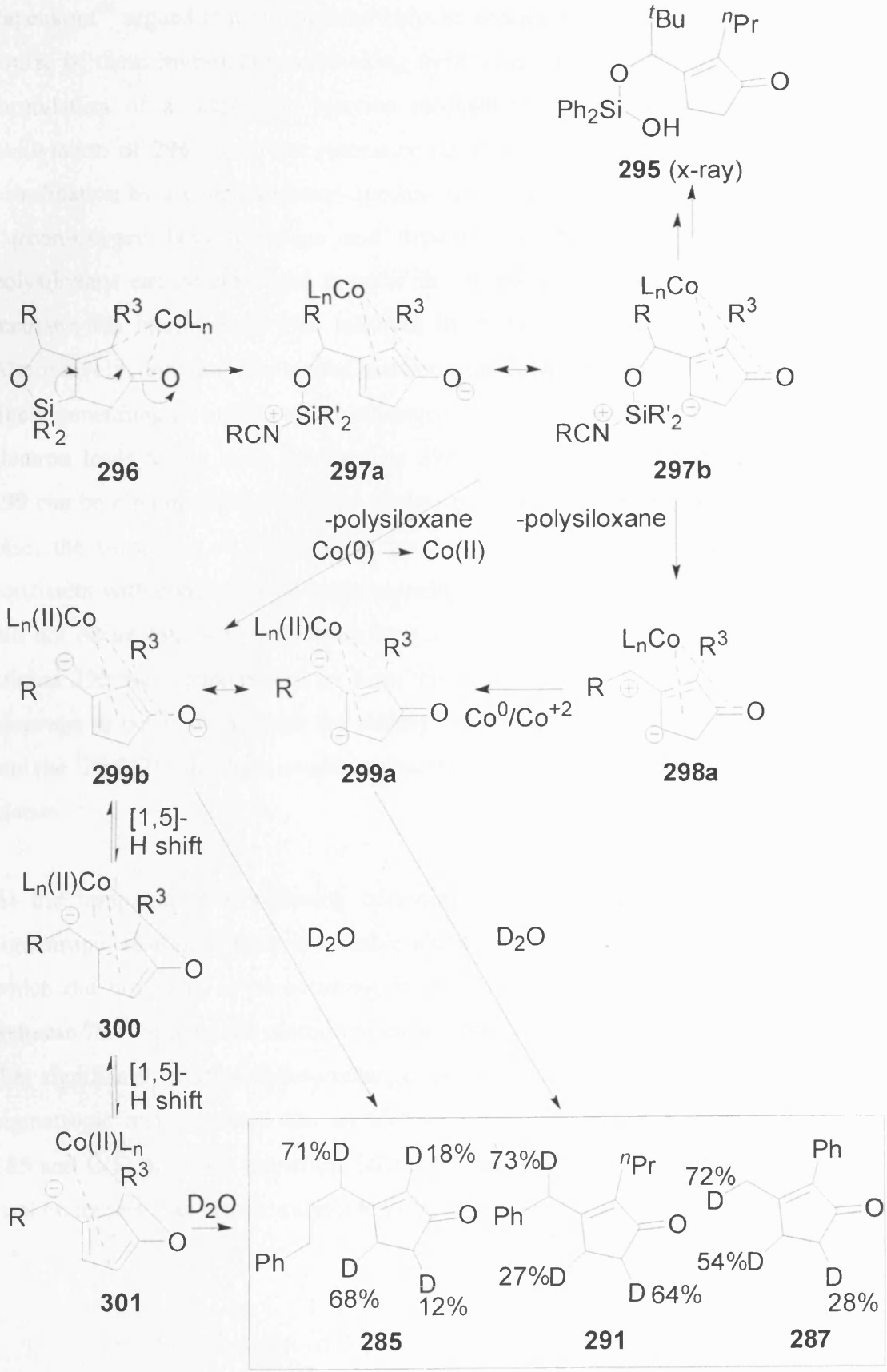
Entry	Substrate	Product & additives	
		1% H_2O	1% D_2O
1	 **283**	 **284,** 45%	 **285,** 8%
2	 **286**	 **215,** 74%	 **287,** 56%
3	 **288,** R = Me **289,** R = Ph	 **290,** 65% **290,** 69%	 **291,** 49% -
4	 **292**	 **293,** 65%	-
5	 **294**	 **295,** 37%	-

Terminal alkynes participate in this reaction albeit with longer reaction times, 24 h in this case (entry 1). Enynes without substitution at the propargylic position (entry 2) also undergo this reaction and both the dimethyl and diphenyl silyl tethers behave in a similar fashion (entry 3). The reaction of pivaldehyde derived enynes **292** and **294** (entries 4 & 5) were anomalous in that no reduction at the propargylic position occurred in these substrates[85]. Bicyclic enones were not observed in any of the above cases. Deuterium labelling was also carried out (**Table 17**, entries 1, 2 & 3) to study the mechanism of this reaction[86].

The enone products in **Table 17** are formally the result of an intermolecular Pauson-Khand reaction of an alkyne with ethylene gas. Pagenkopf[85] argues that this new method is superior to the reaction with ethylene for two main reasons; (i) the reaction does not require high pressures or special equipment and (ii) the use of traceless tether circumvents the regiochemical ambiguity observed in the carbonyl insertion when ethylene is used.

Pagenkopf has proposed a mechanistic hypothesis[86] for this reductive Pauson-Khand reaction of the vinylsilane derived enynes based on deuterium labelling studies and products observed under dry conditions.

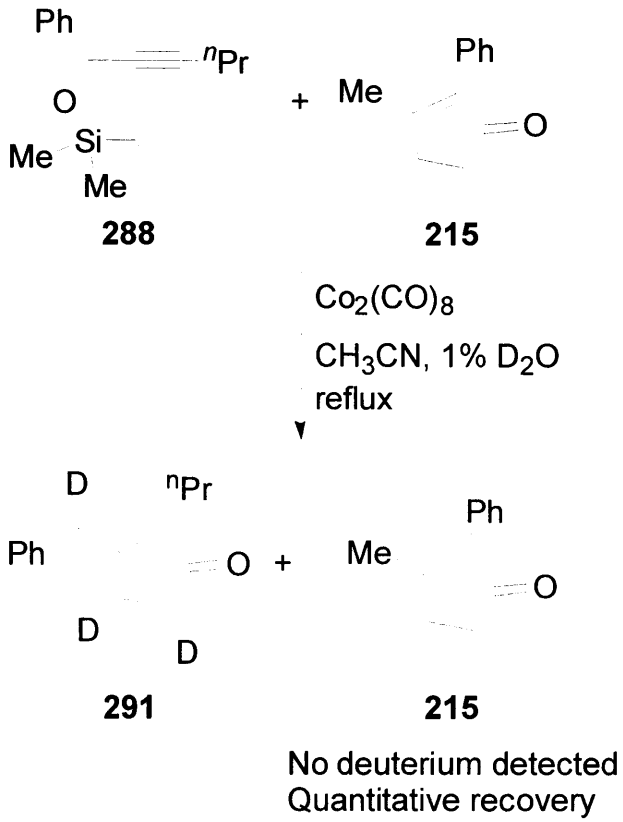
While Lewis acid mediated cleavage of the silicon-carbon bond may be expected with the enones of type **282** (**Scheme 76**), reduction of the carbon-oxygen bond indicates a more complicated mechanism. Simple deuterium labelling studies indicated that the two new enone hydrogens originated from water present in the nitrile solvent at the onset of the reaction and not from the aqueous work up or the nitrile. Given the high pressures required to effect the intermolecular Pauson-Khand reaction with ethylene, tether loss likely occurred after the first carbon-carbon bond forming step in a Magnus like mechanism. A mechanistic hypothesis[86] proposed by Pagenkopf for this reductive Pauson-Khand reaction is depicted in **Scheme 77**.


tBu
nPr
O
O
Ph2Si
OH
295 (x-ray)
R
R3
CoLn
O
O
Si
R'2
RCN
SiR'2
LnCo
296
297a
297b
-polysiloxane
Co(0) → Co(II)
-polysiloxane
Ln(II)Co
299b
299a
298a
Co0/Co+2
[1,5]-
H shift
300
D2O
D2O
[1,5]-
H shift
Co(II)Ln
D2O
301
71%D
D 18%
73%D
nPr
72%
D
Ph
Ph
D
68%
D
12%
27%D
D 64%
54%D
D
28%
285
291
287

Scheme 77

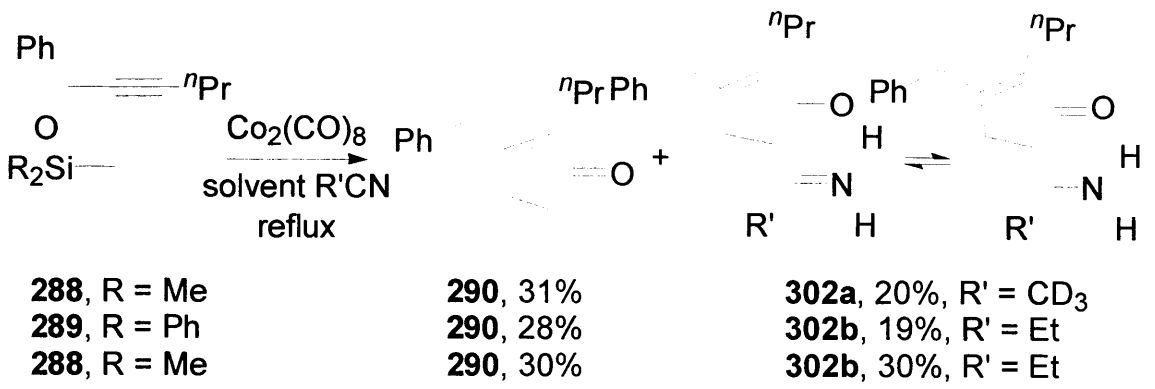
Pagenkopf[86] argued that although no bicyclic enones of type **296** were detected in the course of these investigations, invoking their formation and subsequent demise led to formulation of a reasonable reaction mechanism. According to Pagenkopf, facile desilylation of **296** led to the resonance stabilised enolate **297**. Both ring strain and coordination by a cobalt carbonyl species were considered to facilitate loss of silicon. Carbon-oxygen bond cleavage and departure of the neutral tether remnants as polysiloxane can be envisaged to occur in a stepwise manner giving the trimethylene methane-like intermediate **298**, followed by reduction to the cobalt(II)enolate **299a**. Alternatively, donation of a second electron from cobalt into the enone π system of **297**, likely generating an anion radical, subsequent loss of siloxane and transfer of a second electron leads to the same intermediate **299**. Invocation of the dianionic intermediate **299** can be circumvented simply by enolate protonation prior to siloxane loss. In either case, the formation of a blue-green precipitate during the course of the reaction is consistent with cobalt serving as the reducing agent. Fissure of the carbon-oxygen bond did not occur with the pivaldehyde derived enynes **292** and **294** in **Table 17**, and the silanol **295** was characterised by x-ray crystallography. For the carbon-oxygen bond cleavage to occur in this case the already severe A(1,3) strain between the ^{t}Bu group and the ^{n}Pr C(2) side chain would be exacerbated as the allylic carbon becomes trigonal planar.

At the temperature of refluxing acetonitrile, dienolate tautomerisation by [1,5]-H sigmatropic rearrangements is a viable alternative to intermolecular proton exchange, which did not seem to be occurring in light of the crossover experiments shown in **Scheme 78**.[86] Spiking the reaction of enyne **288** with 1 equivalent of enone **215** showed that significant intermolecular exchange was not occurring (**Scheme 78**). The [1,5]-H sigmatropic rearrangement can account for deuterium incorporation at C(2) of enone **285** and C(5) of all the deuterium labelled enones in **Table 17** (**285**, **287** & **291**). The enol tautomers may also be subject to [1,5]-H sigmatropic rearrangement



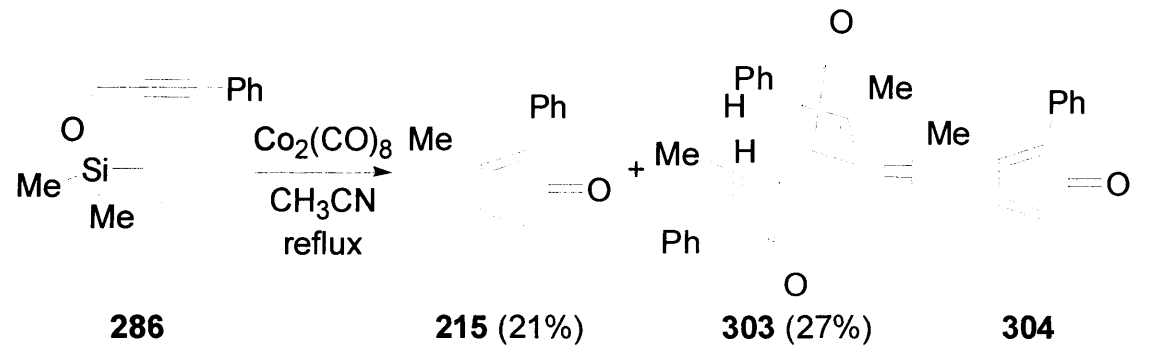
Scheme 78

Obtention of new products along with the expected cyclopentenones under anhydrous conditions was also cited as support for the proposed mechanism.[86] Under anhydrous conditions, interesting new products were obtained along with a decrease in the yield of expected cyclopentenone products. As shown in **Scheme 79**, in dry acetonitrile or propionitrile the benzaldehyde derived enynes **288** and **289** provided the solvent incorporated enones, **302a** and **302b**. Solvent inclusion occurred with either dimethyl or diphenyl substitution at silicon.



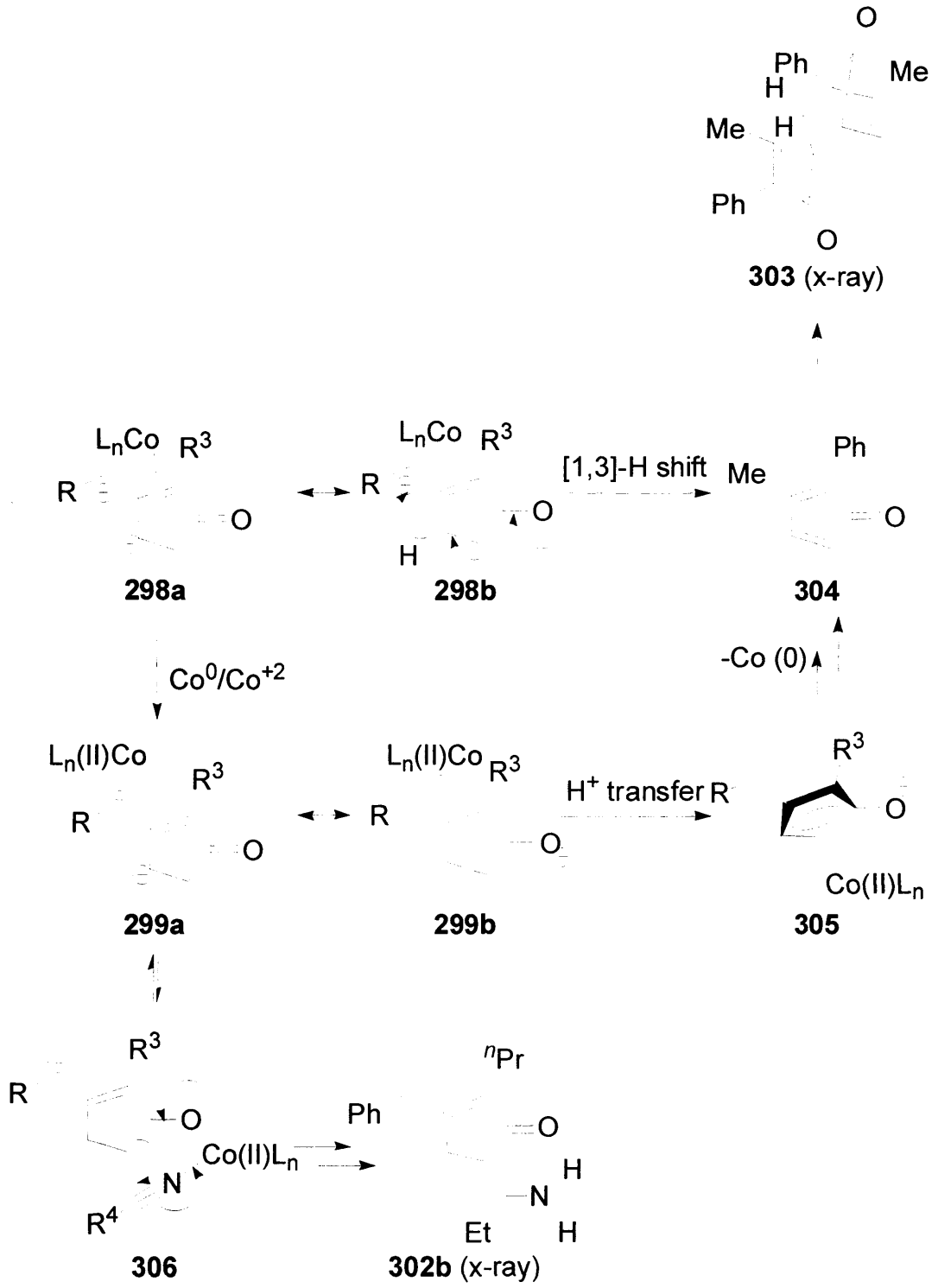
Scheme 79

The reaction of enyne **286** provided the expected enone **215** (21%) and the new tricyclic enone **303** (27%) as shown in **Scheme 80**. Enone **303** appeared to have originated from an intermolecular Diels-Alder reaction of dienone **304**.



Scheme 80

Further elaboration of the proposed mechanism described in **Scheme 77** was used to rationalise the products generated under anhydrous conditions.[86] Nitriles are excellent ligands for various transition metals, and cobalt complexes are particularly effective at activating nitriles to nucleophilic attack. This enhanced nitrile electrophilicity resulting from cobalt coordination may lead to an intramolecular alkylation proceeding through a six-membered transition state (**306**) as shown in **Scheme 81**. The enyne **288** which provided appreciable amounts of the nitrile alkylation products showed the highest amount of deuterium incorporation at C(5) in labelling experiments (**Table 17**, entry 3).



Scheme 81

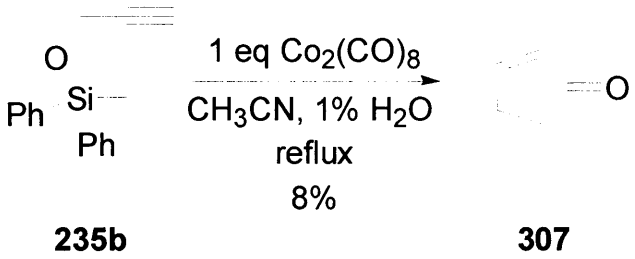
Formation of the Diels-Alder adduct **303** required cyclopentenone oxidation to the dienone **304**. A [1,3]-hydride shift to the exocyclic cation in the zwiterionic intermediate **298b** would lead to **304**. Interestingly only enyne **286** generated appreciable amounts of Diels-Alder product and this was attributed to the formation of a

comparatively unstable carbocation (**298**, R = H). Alternatively it was proposed that a proton transfer from **299b** to form an η^5-CpCo complex such as **305** would also lead to requisite dienone oxidation state.

In conclusion, it was reported that the reductive PKR of tethered vinyl silanes proceeds as usual to the bicyclopentenones, however rapid loss of allylic silane initiates a fragmentation process culminating in reduction of the propargylic carbon. In the absence of protic solvent, the reactive intermediates can attack the nitrile solvent or undergo Diels-Alder dimerisation.

2.1.4 Pauson-Khand reaction of enyne 235b

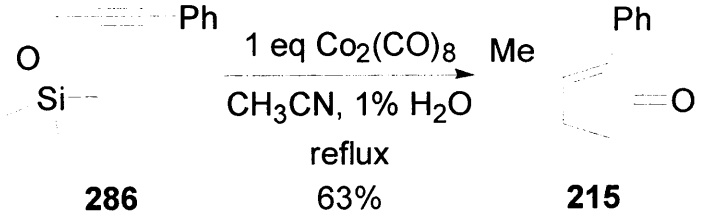
After Pagenkopf's results[85,86] were published we decided to subject our silicon tethered substrate **235b** to Pagenkopf's cyclisation conditions. As can be seen from **Scheme 82**, 3-methylcyclopent-1-enone **307** was obtained in 8% yield. Low yield of this product is attributed in part to its volatile nature. With hindsight, this product could be observed in some unclean fractions obtained after flash column chromatography of reactions we investigated and which are listed in **Table 16**. However it was never isolated or characterised due to contamination from other decomposition products.



235b **307**

Scheme 82

In order to test the reproducibility of Pagenkopf's work[85,86] we synthesised enyne **286** (60% yield) and subjected it to Pagenkopf's reaction conditions (**Scheme 83**). Cyclopentenone **215** was obtained in 63% yield which was comparable to yield reported by Pagenkopf (74%).

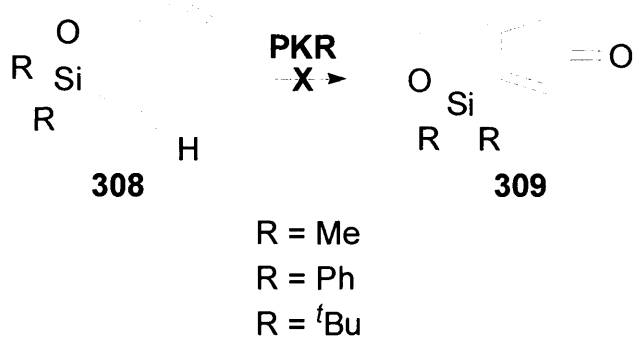


286 63% **215**

Scheme 83

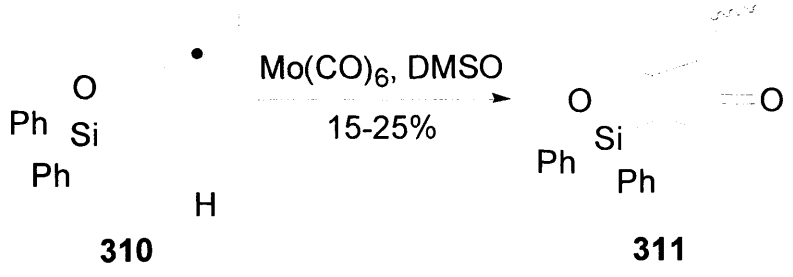
2.1.5 Brummond's silicon-tethered allenic Pauson-Khand reaction

At the same time as Pagenkopf's above mentioned results, Brummond[87] reported the results of a silicon-tethered allenic Pauson-Khand type reaction where normal bicyclic cyclopentenones were obtained. Their attempts to effect the Pauson-Khand cyclisation of cobalt complexes of silyl ethers of type **308** did not yield any cycloadducts (**Scheme 84**). PKR's of these silyl ethers either led to decomplexation or decomposition.[87]



Scheme 84

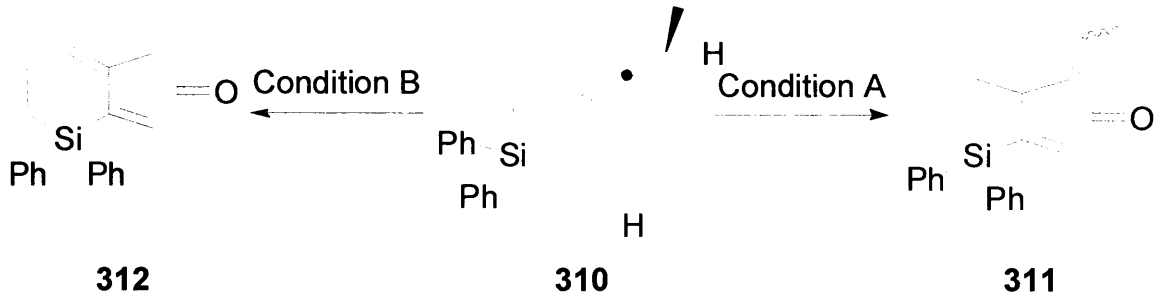
Replacement of the alkene moiety with an allene did give a Pauson-Khand cycloadduct (presumably due to the increased reactivity of the allene) but in consistently low yields (**Scheme 85**). This was partly attributed to the instability of the substrate **310** due to Si-O bond.[87]



Scheme 85

Replacement of the silyl ether tether with a silyl carbon tether resolved the instability problem. Allene-containing substrates such as **310** underwent Pauson-Khand type

cyclisations to give bicycles **311** and **312**, with the selectivity between the two products dependent on the conditions used (**Scheme 86**).[87]



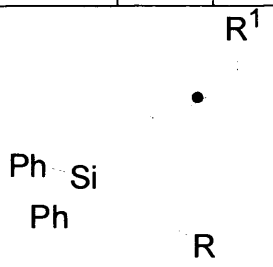
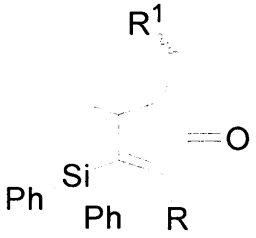
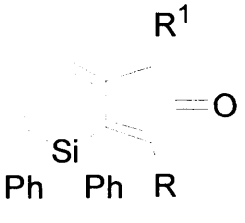
312 **310** **311**

Condition A: 1.2 equiv. $Mo(CO)_6$, DMSO, toluene, 90 °C; Condition B: 5 mol% $[Rh(CO)_2Cl]_2$, CO (1 atm), toluene, 90 °C.

Scheme 86

Cyclisation using stoichiometric molybdenum hexacarbonyl gave the 5,5-fused product **311**, whereas use of 5 mol% of a rhodium(I) complex under an atmosphere of carbon monoxide gave exclusively the 6,5-fused ring system **312**. $Mo(CO)_6$ appears to be intolerant of substitution on the alkyne terminus unlike $[Rh(CO)_2Cl]_2$. As can be seen from **Table 18**, replacement of hydrogen on the alkyne terminus with a butyl (entry 2), trimethylsilyl (entry 3) or phenyl (entry 4) substituent led to no reaction using $Mo(CO)_6$. Substituting a longer alkyl chain on the allene (entry 5) gave only a 36% yield of cycloadduct **323**. Alkynyl allene (entry 6) gave α-methylene cyclopentenone **326** in 48% yield. Use of 5 mol% $[Rh(CO)_2Cl]_2$ on all of the above mentioned substrates (except **325**) gave moderate to good yields of 6,5 fused bicycles.

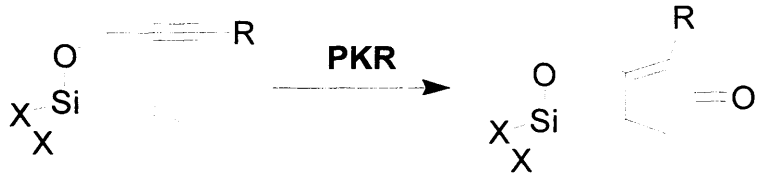
Table 18. Brummond's silicon-tethered allenic PKR[87]

Entry	Substrate	R	R^1	5,5-product [a] Yield (%)	6,5-product [b] Yield (%)
					
1	**310**	H	CH_3	**311**, 64	**312**, 64
2	**313**	Bu	CH_3	**314**, 0	**315**, 75
3	**316**	TMS	CH_3	**317**, 0	**318**, 74
4	**319**	Ph	CH_3	**320**, 0	**321**, 51
5	**322**	H	C_5H_{11}	**323**, 36	**324**, 55
6	**325**	H	H	**326**, 48	-

[a] Conditions: 1.2 equiv. $Mo(CO)_6$, DMSO, toluene, 90 °C, [b] Conditions: 5 mol% $[Rh(CO)_2Cl]_2$, CO(1atm), toluene, 90 °C.

2.2 Allylsilane-derived enynes

In the light of the failure of vinylsilane derived enynes to undergo Pauson-Khand reaction and of Pagenkopf's proposed mechanism[85,86] for the reductive PKR of vinyl silane derived enynes, we decided to synthesise allylsilane-derived enynes as substrates for the Pauson-Khand reaction. It was expected that the extra carbon in the alkene chain would prevent the loss of the silicon tether, (section 2.1.3, **Scheme 77**, p. 95), and hence lead to bicyclic cyclopentenones of type **328** in **Scheme 87**.



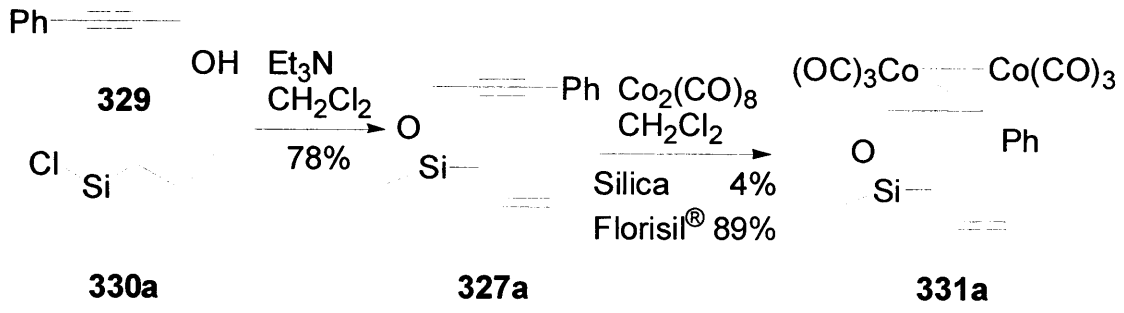
327a, X = CH_3
327b, X = Ph

328a, X = CH_3
328b, X = Ph

Scheme 87

2.2.1 Synthesis of substrate 327a

Due to the commercial availability of allylchlorodimethylsilane **330a**, we decided to synthesise the allyldimethylsilane-derived enyne **327a** and to carry out optimisation of PKR conditions on its dicobalt hexacarbonyl complex **331a** rather than its diphenyl equivalent (**Scheme 88**). This was despite the potential instability of dimethylsiloxy derivatives and the associated problems of purification by flash column chromatography on silica. We hoped to establish the optimum set of conditions for cyclisation of enyne **327a** to bicyclic cyclopentenone **328a** and then subject a range of substrates, containing substituents offering different electronic and steric properties at the alkyne and alkene positions, to the optimised Pauson-Khand cyclisation conditions for these substrates.



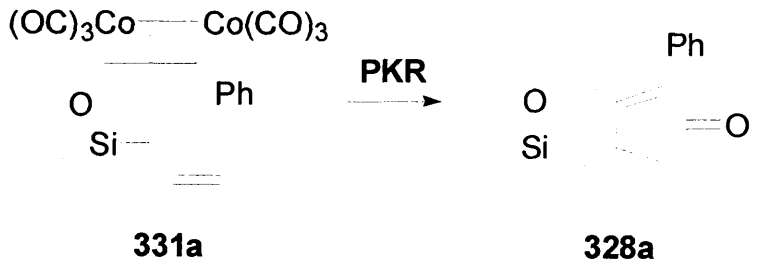
Scheme 88

Silylation of 3-phenyl-2-propyn-1-ol **329** using allylchlorodimethylsilane **330a** in the presence of triethylamine in dichloromethane led to enyne **327a** in 78% yield after purification by flash column chromatography using silica as solid support (**Scheme 88**). This was in stark contrast to vinylsilane-derived enyne **235b**, which decomposed completely on silica (section 2.1.1, p. 86).

2.2.2 Pauson-Khand reaction of dimethylsilyl ether 327a

The dicobalt hexacarbonyl complex **331a** of enyne **327a** was synthesised by stirring the enyne **327a** and dicobalt octacarbonyl in dichloromethane at room temperature (**Scheme 88**). The yield of the dicobalt hexacarbonyl complex **331a** was dependent on the solid support used for purification. Purification using silica as solid support led to decomposition of the complex whereas purification using Florisil®, which is neutral, led to the desired complex in 89% yield. Complex **331a** also decomposed on gentle warming therefore solvent was removed *in vacuo* at room temperature. The ^{1}H NMR spectrum of dicobalt hexacarbonyl complex **331a**, although broad, showed that the OCH_2 protons had shifted downfield from 4.55 ppm in the starting enyne **327a** to 5.01 ppm in the dicobalt hexacabonyl complex **331a**.

The dicobalt hexacarbonyl complex **331a** was subjected to a wide range of Pauson-Khand cyclisation conditions from literature and the results are shown in **Table 19**.



331a **328a**

Scheme 89

Table 19. Pauson-Khand reactions of DCHC 331a

Entry	PKR Conditions	Yield (%)[a]
1	Toluene, reflux	40
2	CH_3CN, reflux	39
3	CH_3CN, 1% H_2O, reflux	33
4	H_2O, CTAB, Celite, 70 °C	0
5	3.5 eq $CyNH_2$, 1,2-DCE, reflux	0
6	3.5 eq *n*BuSMe, 1,2-DCE, reflux	72

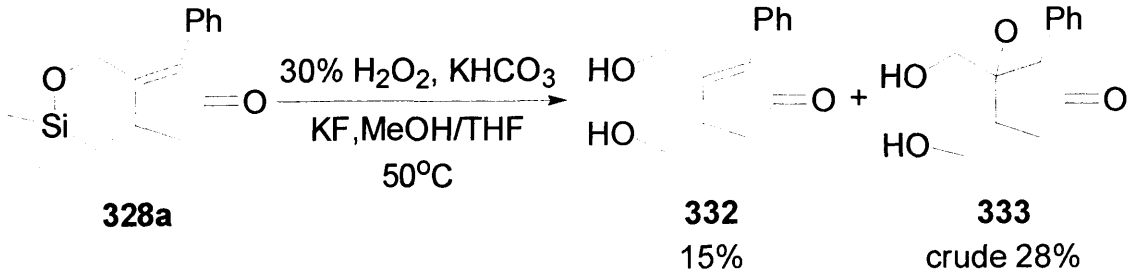
[a] Florisil® was used for purification by flash column chromatography.

As discussed in introduction, (section 1.3.1, p. 24), yields of Pauson-Khand reactions generally increase in polar solvents such as acetonitrile compared to toluene. However heating the dicobalt hexacarbonyl complex **331a**, to reflux in toluene and acetonitrile[91] gave comparable yields of the bicycle **328a**, 40% and 39% respectively (entries 1 & 2). Pagenkopf's cyclisation conditions[86] were also attempted in order to see if the yields of the PKR of allylsilane derived enynes, like vinylsilane derived enynes, improved under these conditions. Addition of 1% H_2O to the reaction mixture led to lowering of the yield from 39% to 33% (entry 3), however this may be due to the decomposition of the dicobalt hexacarbonyl complex **331a** or the bicycle **328a** in H_2O. Thermal Pauson-Khand reaction in H_2O[35] (entry 4) and amine promoted Pauson-Khand reaction[28] (entry 5) did not lead to the desired bicycle **328a**. ^1H NMR spectra of the fractions obtained after flash column chromatography showed that the decomplexation of cobalt was occurring and impure enyne **327a** was recovered along with unidentifiable products. The sulfide promoted Pauson-Khand reaction[29] gave the best yield of 72% for the cyclisation of the dicobalt hexacarbonyl complex **331a** to the bicyclic cyclopentenone

328a (entry 6). As can be seen from **Scheme 23** (section 1.3.4, p. 36), sulfide promoted PKR seems to be a milder method than the amine promoted PKR.

Although the dicobalt hexacarbonyl complex **331a** undergoes Pauson-Khand reaction in moderate to good yields, several problems were encountered with the purification of the Pauson-Khand reactions described above. As discussed in the previous section, presence of paramagnetic cobalt impurities made the analysis of the crude reaction mixtures by ^{1}H NMR impossible. The complete decomposition of the bicycle **328a** on silica led to Florisil® being used as the solid support for flash column chromatography but the fractions from the column were spotted on silica plates which showed the decomposition products as well as the desired bicycle **328a**. Also the degree of separation of impurities from the desired compound **328a** on Florisil® was very poor and gradient elution was used to separate the product from other impurities.

We therefore decided to attempt to remove the silicon tether of the bicycle **328a** by Tamao oxidation[81] to form the diol **332**. It was hoped that once conditions for the cleavage of the silicon tether were established, the crude Pauson-Khand reaction mixtures would be subjected directly to these conditions, which would solve any purification problems posed by the presence of a silyl ether in the bicycle.



328a **332** 15% **333** crude 28%

Scheme 90

Tamao oxidation[92] of bicycle **328a** led to not only the expected diol **332** (15%) but also epoxydiol **333** in 28% crude yield. This was due to the presence of basic H_2O_2, which led to the epoxidation of the double bond present in the bicycle **328a** along with the

cleavage of the silicon tether. All attempts to purify the epoxydiol **333** by flash column chromatography or by preparative tlc were unsuccessful.

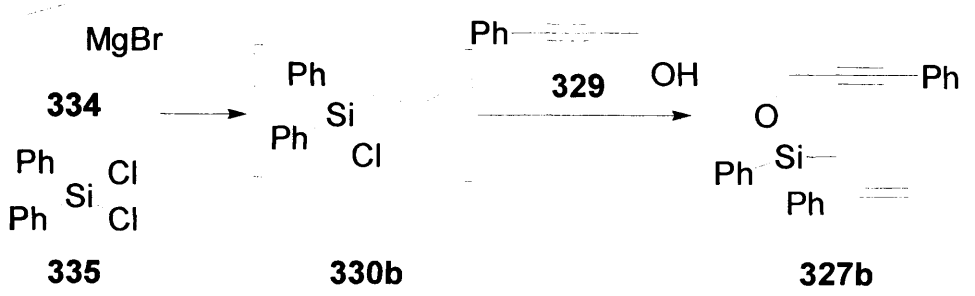
Attempts at removal of the tether by tetra-*n*-butylammonium fluoride (TBAF) led to unidentifiable and inseparable mixtures of compounds.

Due to the instability of the model enyne **327a**, dicobalt hexacarbonyl complex **331a** as well as the bicycle **328a** on silica and perhaps even to some of the Pauson-Khand reaction conditions, we decided to synthesise enyne **327b** and to study its Pauson-Khand reaction. Diphenylsilyl derivatives are known to be more robust than their dimethyl equivalents and can be purified using silica.

2.2.3 Synthesis of diphenylsilyl ether 327b

The synthesis of allyldiphenyl(3-phenylprop-2-ynyloxy)silane **327b** was not straightforward due to the lack of commercial availability of allylchlorodiphenylsilane **330b**. We initially decided to synthesise allylchlorodiphenylsilane **330b** by Grignard addition of allylmagnesium bromide **334** to dichlorodiphenylsilane **335** using a published procedure[93]. The ^{1}H NMR spectrum of the crude reaction mixture showed too many aromatic protons compared to protons of the alkene. Chlorosilane **330b** could not be isolated or purified either by reduced pressure distillation or by flash column chromatography. We attributed this finding to the moisture and acid sensitive nature of allyldiphenylchlorosilane **330b**. Addition of freshly prepared allylmagnesium bromide **334** to dichlorodiphenylsilane **335** did not lead to allyldiphenylchlorosilane **330b**. The ^{1}H NMR spectra in some cases contained small amounts of desired chlorosilane **330b**, however it could not be isolated by reduced pressure distillation or by flash column chromatography.

We therefore decided to synthesise the desired enyne **327b** in one-pot without any purification of allylchlorodiphenylsilane **330b**. We first attempted to synthesise the enyne **327b** using the sequence of reactions shown in **Scheme 91**.



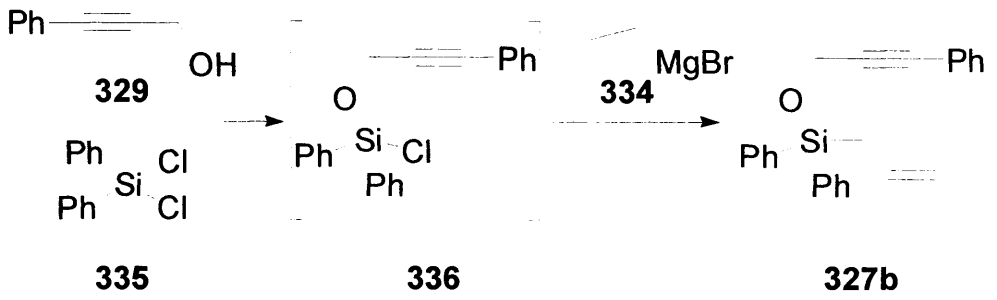
Scheme 91

Table 20. Conditions used for attempted synthesis of 327b

Entry	Solvent for Grignard addition	Conditions for silylation of alcohol **329**
1	$PhCH_3$, rt[93]	Et_3N, CH_2Cl_2, 0 °C to rt[94]
2	THF, rt	Et_3N, THF, 0 °C to rt[95]
3	THF, -78 °C to rt	Imidazole, THF, reflux
4	THF, rt	NaH, THF, rt
5	THF, -78 °C to rt	Imidazole, DMF, rt
6	$PhCH_3$, rt	Et_3N, 10 % DMAP, CH_2Cl_2, 0 °C to rt

The desired enyne **327b** could not be synthesised by any of the procedures listed in **Table 20**. Toluene and THF were tried as solvents to carry out the Grignard addition and several bases were tried for the silylation of the alcohol **329**, however none gave the desired enyne **327b**. (Conditions described in entry 1 gave the desired product in 6% irreproducible yield).

Carrying out the reaction with the silylation of alcohol **329** first followed by Grignard addition as described in **Table 21** for **Scheme 92** again did not yield any desired product **327b**.



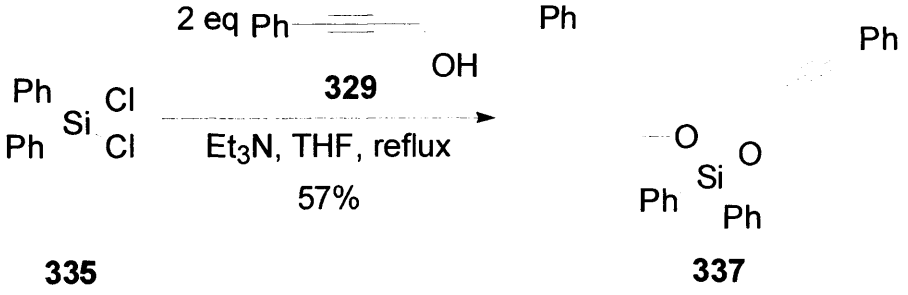
Scheme 92

Table 21. Conditions used for attempted synthesis of 327b

Entry	Conditions for silylation of alcohol **329**	Conditions for Grignard addition
1	Et_3N, THF, 0 °C to rt	THF, rt
2	Et_3N, THF, reflux[95]	THF, rt

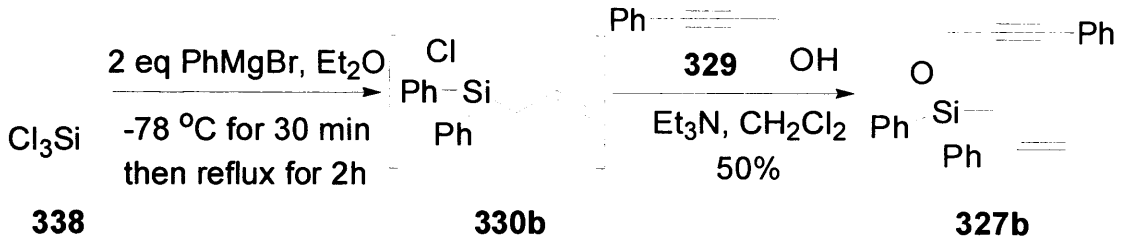
Both of the conditions described in **Table 21** did not lead to the desired enyne **327b**.

Successful disilylation of alcohol **329** with dichlorodiphenylsilane **335** to synthesise compound **337** (**Scheme 93**)[95] showed that the Grignard addition in the above sequence of steps was not taking place effectively.



Scheme 93

We then decided to synthesise the chlorosilane[96] **330b** from commercially available allyltrichlorosilane **338** and to use it crude without further purification in one pot using the sequence of steps indicated in **Scheme 94**.[94,96]



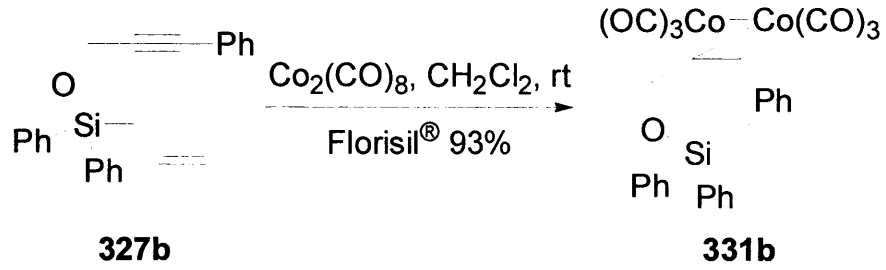
338 **330b** **327b**

Scheme 94

Two equivalents of phenylmagnesium bromide were added to a solution of allyltrichlorosilane **338** in ether at -78 °C. The resulting reaction mixture was stirred at -78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 hours. The resulting solution of allyldiphenylchlorosilane **330b**[96] was added dropwise to a solution of phenylpropargyl alcohol **329** and triethylamine in dichloromethane at 0 °C, then stirred at room temperature overnight[94]. The desired enyne **327b** was obtained in 50% yield over two steps. The ^{1}H NMR spectrum of the crude enyne **327b** showed mostly desired product, however the yield after purification was lower due to decomposition of the enyne **327b** on silica. Nevertheless, silica was preferred for flash column chromatography to Florisil® due to better separation of the product from other impurities.

2.2.4 Pauson-Khand reaction of diphenylsilyl ether 327b

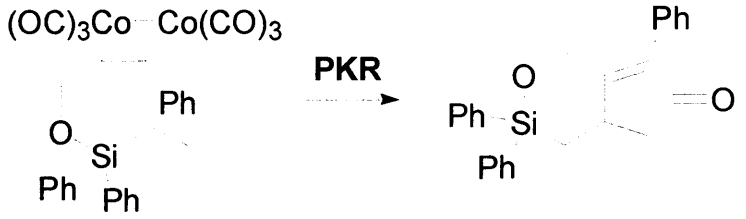
The dicobalt hexacarbonyl complex **331b** of enyne **327b** was synthesised by stirring the enyne **327b** and dicobalt octacarbonyl in dichloromethane at room temperature (**Scheme 95**). The deep red dicobalt hexacarbonyl complex **331b** could be purified by flash column chromatography using Florisil® in 93% overall yield. The ^{1}H NMR spectrum of the dicobalt hexacarbonyl complex **331b** again showed a downfield shift of the OCH_2 protons to 5.12 ppm from 4.63 ppm in the starting enyne **327b**.



327b **331b**

Scheme 95

The dicobalt hexacarbonyl complex **331b** was then subjected to a wide range of Pauson-Khand cyclisation conditions. The Pauson-Khand reaction of dicobalt hexacarbonyl complex **331b** yielded the bicycle **328b** **(Scheme 96)** and results are summarised in **Table 22.**



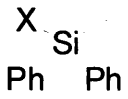
331b **328b**

Scheme 96

Table 22. Pauson-Khand reactions of 331b

Entry	Conditions	Yield (%)
1	Toluene, reflux	28
2	CH_3CN, reflux	35
3	CH_3CN, 1% H_2O, reflux	48
4	NMO, CH_2Cl_2, rt	45
5	Toluene, 4Å Molecular Sieve powder, reflux	16
6	Toluene, 4Å Molecular Sieve powder, NMO, rt	0
7	3.5 eq $CyNH_2$, 1,2-DCE, reflux	0
8	Florisil®, 50 °C, Air	0
9	Silica, 50 °C, Air	0
10	3.5 eq *n*-BuSMe, 1,2-DCE, reflux	70

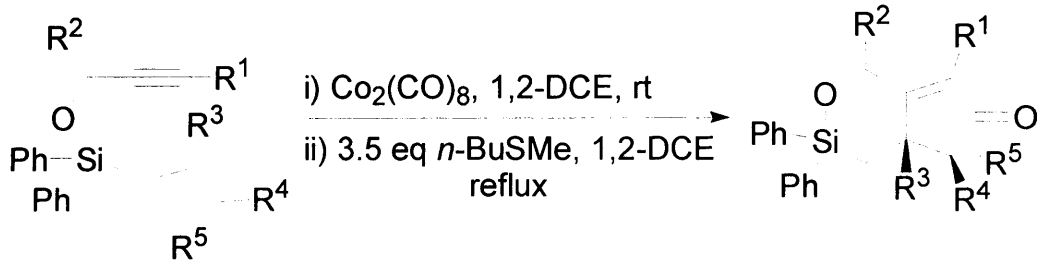
Heating the dicobalt hexacarbonyl complex **331b** to reflux in toluene led to the bicycle **328b** in 28% yield (**Table 22**, entry 1). The use of polar solvent acetonitrile[91] led to an improvement in the yield to 35% (**Table 22**, entry 2). A higher yield of 48% for bicycle **328b** (**Table 22**, entry 3) was obtained when Pagenkopf's conditions[86] were used for PKR of dicobalt hexacarbonyl complex **331b**. Use of NMO[25] for the promotion of PKR of dicobalt hexacarbonyl complex **331b** yielded bicycle **328b** in 45% yield (**Table 22**, entry 4). Some cleavage of the Si-O bond was also observed when NMO was used as a promoter of the reaction. Zeolites such as molecular sieves are also known to promote Pauson-Khand reactions (section 1.3.6, p. 39). Perez-Castells[34] reported two different reaction conditions for promotion of the reaction by molecular sieves, one in the absence of amine-*N*-oxide and one in its presence. The reaction yields tended to be higher in the presence of both molecular sieves and TMANO together in the reaction mixture. However in the case of dicobalt hexacarbonyl complex **331b**, (i) in the presence of molecular sieves 16% of the desired bicycle **328b** was obtained (entry 5) and (ii) use of both molecular sieves and NMO did not yield any desired bicycle **328b** (entry 6). In the case where only molecular sieves were used to promote the reaction, the bicycle **328b** could not be completely separated from unknown impurities and hence the yield is low. In the case where both molecular sieves and NMO were used as promoters of the reaction (entry 6), cleavage of the Si-O bond was observed. Some cleavage of the Si-O bond was also observed when only NMO was used as a promoter of the reaction (entry 4). Hence this cleavage may possibly be due the presence of NMO in the reaction mixture. The cleaved product **339** in **Figure 7** could not be fully characterised as the identity of X could not be established. Use of cyclohexylamine as a promoter[28] (entry 7) led to no reaction. Si-O bond cleavage was again observed in this case, however the decomposition product could not be fully characterised. Use of dry state adsorption conditions (DSAC)[31] using either Florisil® (entry 8) or silica (entry 9) as solid supports again did not yield any of the desired cycloadduct **328b**. Mixtures of unidentifiable and inseparable products were obtained. The best yield of 70% was obtained in the case of sulfide promoted Pauson-Khand reaction[29] (**Table 22**, entry 10). This was comparable to the reaction of dimethylsilyl dicobalt hexacarbonyl complex **331a**, which led to 72% of the bicycle **328a** under the same conditions (**Table 19**, entry 6).



339

Figure 7

In the light of the results in **Table 22** and described above, the more robust diphenylsilylethers were selected for the study of scope of this silicon tethered Pauson-Khand reaction. We decided to synthesise a range of allyldiphenylsilyl propargyl ethers, with substituents offering different properties at both the alkyne and alkene moiety. The sulfide promoted PKR was chosen as the method of choice for the Pauson-Khand reaction of these substrates as the highest yields of bicycles **328a** and **328b** were obtained under these conditions. It was hoped that PKR of these substrates would lead to bicyclic enones **328c-328j** as shown in **Scheme 97**.



327c-327j **328c-328j**

Scheme 97

2.2.5 Synthesis of Substrates 327c-327j

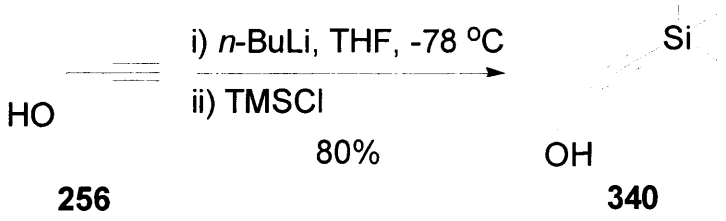
All substrates shown in **Table 23** were prepared using a similar procedure[94,96] as for the synthesis of diphenylsilyl ether **327b**, as illustrated in **Scheme 94**. It was hoped that Pauson-Khand reaction of these substrates would lead to cycloadducts **328c-328j** (**Scheme 97**).

Table 23. Substrates synthesised for PKR

Entry	Substrates	R^1	R^2	R^3	R^4	R^5	Yield (%)
1	**327c**	H	H	H	H	H	18[b]
2	**327d**	Me	H	H	H	H	32[a]
3	**327e**	TMS	H	H	H	H	29[b]
4	**327f**	Ph	Ph	H	H	H	47[c]
5	**327g**	Ph	Me	H	H	H	63[c]
6	**327h**	Ph	H	Me	H	H	39[b]
7	**327i**	Ph	H	Me	H	Me	12[c]
8	**327j**	Ph	H	H	Me	H	29[b]

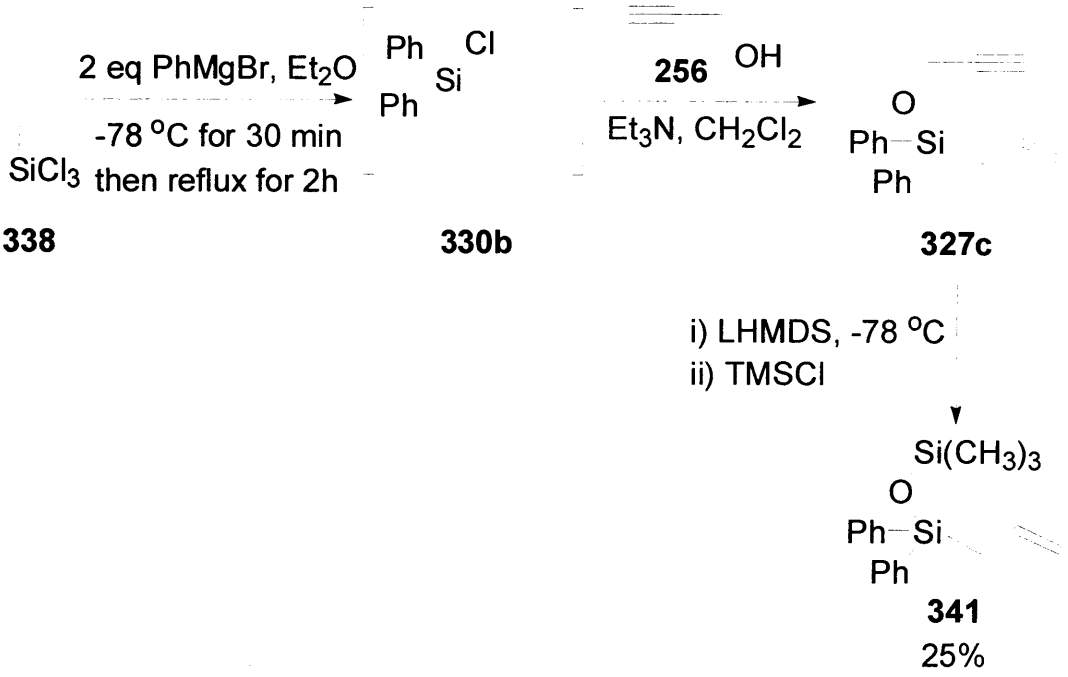
[a] Purification using silica [b] Purification using Florisil® [c] Purification using deactivated grade (III) alumina.

3-Trimethylsilanylprop-2-ynyl-1-ol **340**, required for the synthesis of **327e** was prepared by deprotonation of propargyl alcohol **256** using *n*-BuLi followed by quenching with chlorotrimethylsilane (80% yield) and is illustrated in **Scheme 98**.[97]



Scheme 98

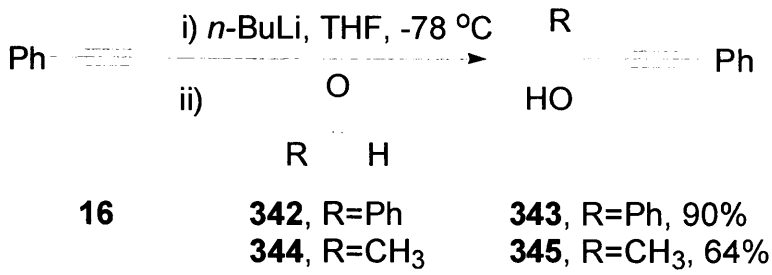
The synthesis of **327e** was achieved after a small variation to the general procedure illustrated in **Scheme 94**. For the other substrates described in **Table 23**, allylchlorodiphenylsilane **330b** was added to a solution of alcohol and triethylamine in CH_2Cl_2 at 0 °C and the resulting reaction mixture was then warmed to room temperature overnight. However this procedure did not yield the desired substrate **327e**, instead a complex mixture of unidentifiable products was obtained. Repeating the above procedure several times did not lead to any isolable products. We then decided to synthesise **327e** via the deprotonation of the crude substrate **327c** using LHMDS followed by addition of chlorotrimethylsilane. However this procedure led to the isolation of compound **341** in 25% yield over 3 steps as illustrated in **Scheme 99**.



Scheme 99

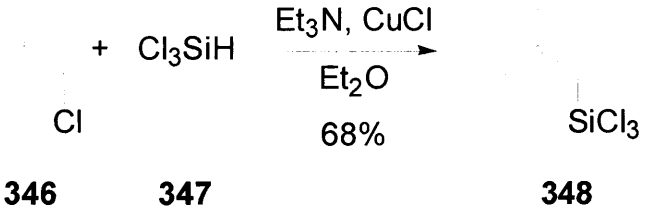
However **327e** was obtained in 29% yield when the allylchlorodiphenylsilane **330b** was added to a solution of 3-trimethylsilanylprop-2-yn-1-ol **340**, 4-dimethylaminopyridine and triethylamine in CH_2Cl_2 at -78 °C, stirred for 1 h at -78 °C and then allowed to warm to room temperature over 2 days. Considerable decomposition of **327e** seemed to be occurring upon purification.

Secondary propargylic alcohols required for the synthesis of **327f** and **327g** were prepared using published literature procedure[98]. Deprotonation of phenylacetylene **16** using *n*-BuLi followed by the addition of benzaldehyde **342** yielded 1,3-diphenylprop-2-yn-1-ol **343** (for the synthesis of **327f**) in 90% yield. Addition of acetaldehyde **344** to deprotonated phenylacetylene led to 4-phenylbut-3-yn-2-ol **345** (for the synthesis of **327g**) in 64% yield (**Scheme 100**). **327f** and **327g** were obtained in 47% and 63% yield (**Table 23**, entries 4 & 5 respectively).



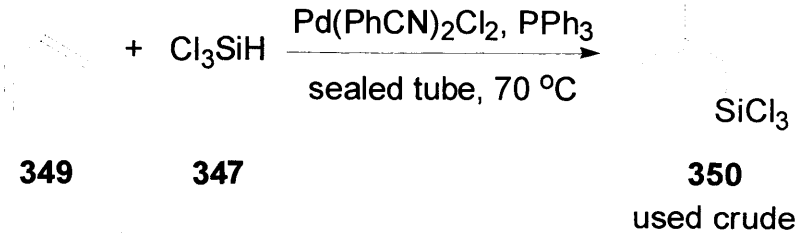
Scheme 100

Trichlorosilanes required for the syntheses of **327h**, **327i** and **327j** in which the alkene moiety is substituted, were not commercially available and were synthesised using literature procedures. Trichloro(2-methylallyl)silane[99] **348** was prepared by the addition of a mixture of trichlorosilane **347** and 2-methallyl chloride **346** to a mixture of triethylamine and cuprous chloride (**Scheme 101**). The required compound **348** was purified by reduced pressure distillation in 68% yield and subsequently converted to **327h** in 39% yield (**Table 23**, entry 6).



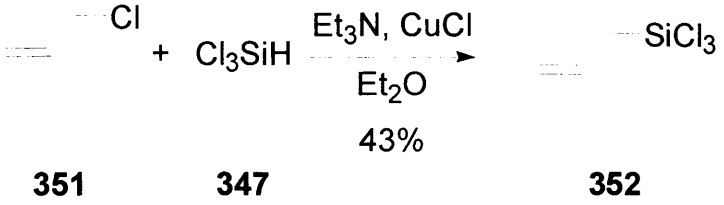
Scheme 101

(*Z*)-Trichloro(2-methylbut-2-enyl)silane[100] **350** was prepared by heating trichlorosilane **347**, isoprene **349**, triphenylphosphine and bis(benzonitrile)palladium(II)chloride ($Pd(PhCN)_2Cl_2$) in a sealed tube at 70 °C (**Scheme 102**). The ^1H NMR spectrum showed the crude product **350** to be clean and it was used without further purification, hence the yield (12%) quoted for the synthesis of **327i** (**Table 23**, entry 7) is over three steps.



Scheme 102

(*E*)-Crotyltrichlorosilane[99] **352** was prepared, using the same procedure as for the synthesis of trichloro(2-methylallyl)silane **348**, from crotyl chloride **351**, trichlorosislane **347** triethylamine and cuprous chloride (**Scheme 103**). Crotyl chloride **351** was only available as mixture of 1 : 6 *cis* : *trans* isomers. Silane **352** was purified by reduced pressure distillation and was obtained in 43% yield and as a 1 : 6 mixture of *cis* : *trans* diastereoisomers which were used for the synthesis of **327j** without separation. Surprisingly only *trans*-but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane **327j** was isolated from the reaction for the synthesis of **327j**. The ^{1}H NMR spectrum did not show any evidence of *cis*- but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane.



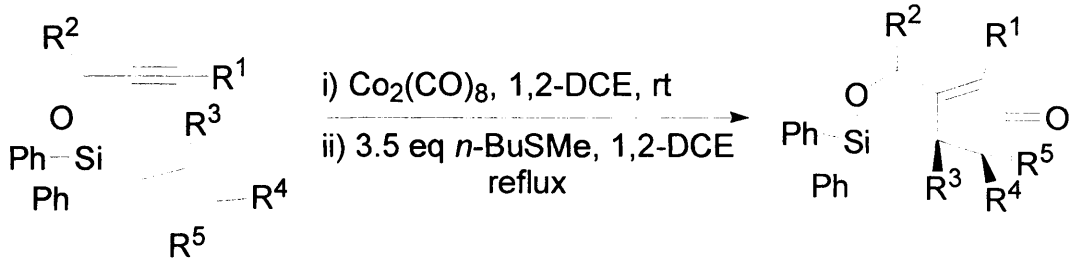
Scheme 103

As can be seen from the **Table 23**, only **327d** could be purified using silica. Other substrates were purified using either deactivated grade (III) alumina or Florisil® as solid supports for flash column chromatography. These solid supports were not interchangeable for these substrates, *e.g.* **327c** decomposed on both alumina and silica and could only be purified using Florisil®. Considerable decomposition seemed to be occurring on all three solid supports as ^{1}H NMR spectra of crude products suggested that higher yields of desired products were present compared to the yields actually obtained.

We decided to synthesise di*tert*-butylsilyl propargyl ethers to see if they would be more stable to purification by flash chromatography. Unfortunately we could not synthesise these ethers. Allyldi*tert*-butylchlorosilane could not be prepared by addition of *t*-BuLi or *t*-BuMgCl to allyltrichlorosilane. One pot synthesis of di*tert*-butylsilyl propargyl ethers using a similar procedure as for the synthesis of diphenylsilyl propargyl ethers also failed to yield the desired enynes.

2.2.6 Results of Pauson-Khand studies for substrates 327c-327j

The results for the Pauson-Khand reaction of substrates synthesised during the course of our studies are listed in **Table 24** for **Scheme 104**.



327c-327j **328c-328j**

Scheme 104

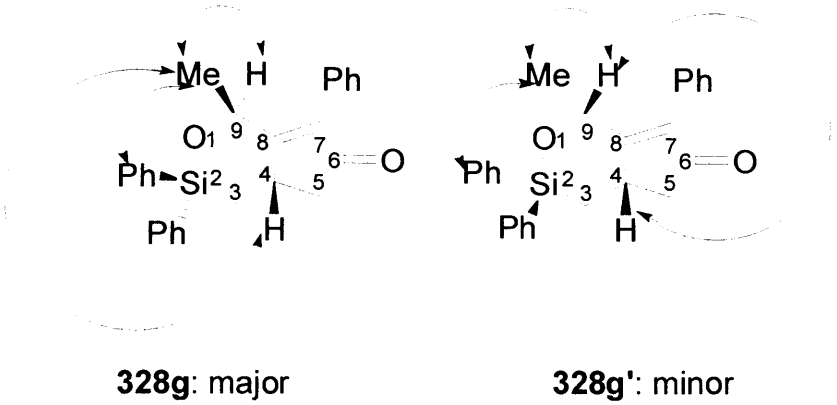
Table 24. Results of PKR of substrates 327c-327j

Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Yield (%) of cycloadduct
1	**327c**	H	H	H	H	H	**328c**, 0[a,b]
2	**327d**	Me	H	H	H	H	**328d**, 38[a]
3	**327e**	TMS	H	H	H	H	**328e**, 14[a]
4	**327f**	Ph	Ph	H	H	H	**328f**, 0[b]
5	**327g**	Ph	Me	H	H	H	**328g**, 9[a,c]
6	**327h**	Ph	H	Me	H	H	**328h**, 0[a]
7	**327i**	Ph	H	Me	H	Me	**328i**, 0[a]
8	**327j**	Ph	H	H	Me	H	**328j**, 33[a]

[a] Purification using Florisil® [b] Purification using deactivated grade(III)alumina [c] The product was obtained as 1.5 : 1 mixture of diastereomers.

Unfortunately, few of the compounds synthesised proved to be good substrates for the Pauson-Khand reaction. A silyl ether derived from propargyl alcohol (**327c**, entry 1) did not undergo Pauson-Khand cycloaddition at all. Inseparable and unidentifiable product mixtures were obtained after flash column chromatography using either alumina or Florisil®. The ^{1}H NMR spectrum of one of the fractions from a column on alumina showed the presence of protons associated with the alkene, but there was no evidence of protons associated with the alkyne moiety. This suggested that the decomposition of starting material via the cleavage of Si-O bond was occurring, either during the reaction or upon chromatography. An alkyne bearing a terminal methyl (**327d**, entry 2) or trimethylsilyl substituent (**327e**, entry 3) afforded the bicycles **328d** and **328e** in relatively poor yields of 38 % and 14 % respectively. For the PKR of **327e**, some unclean starting enyne **327e** was recovered from the column (23%). As described in section 2.2.5 (p. 115), the starting enyne **327e** decomposes easily and hence may account for the poor yield of the bicycle **328e**. The bicycle **328e** may also be decomposing on the column due to the presence of a trimethylsilyl substituent, although no decomposition products were isolated.

We then investigated the effect of substitution at the propargylic position of these substrates. Two substrates **327f** (with a Ph substituent at the propargylic position) and **327g** (with a Me substituent at the propargylic position) were subjected to the sulfide promoted Pauson-Khand reaction. **327f** (entry 4) did not give any of the desired product. Starting enyne **327f** was recovered from the reaction mixture (23%) along with various unidentifiable products. The substrate with the propargylic methyl group (**327g**, entry 5) underwent cyclisation in very poor yield (9%) and with very low diastereoselectivity (1.5 : 1 in favour of the *exo* diastereomer). The two diastereomers (**328g** and **328g'** in **Figure 8**) could not be separated by flash column chromatography. The relative stereochemistry of the two diastereomers was established using one-dimensional NMR experiments (^{1}H spectra and NOE) on the isolated mixture.

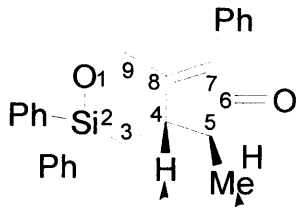


328g: major **328g'**: minor

Figure 8

In the NOE experiment of the major isomer (**328g**) irradiation of H-9 generated an enhancement of some aromatic protons and of the methyl group. No enhancement of H-4 was observed. Irradiation of the methyl signal led to an enhancement in the signal of H-4 indicating a *trans* relative stereochemistry between H-9 and H-4. In the NOE experiment of minor isomer (**328g'**), irradiation of H-9 led to enhancement of some aromatic protons as well as of H-4. Irradiation of the methyl signal led only to enhancement of H-9 and crucially no positive enhancement of H-4 was observed indicating a *cis* relative stereochemistry between H-4 and H-9.

The tolerance of this silicon-tethered Pauson-Khand reaction to substitution on the alkene double bond was also studied. Of the three substrates prepared (**327h**, **327i** and **327j**) only **327j** (entry 8) underwent Pauson-Khand cyclisation to yield cycloadduct **328j** in 33% yield. Starting material **327j** was also recovered in 13% yield from the reaction mixture. Only the isomer shown in **Figure 9** below was isolated from the reaction mixture showing, as expected, the preservation of *trans* relative stereochemistry of H-4 and H-5 under the reaction conditions tested. In the NOE experiments, positive enhancement between H-4 and the methyl group was observed indicating the *trans* relative stereochemistry between H-4 and H-5.



328j

Figure 9

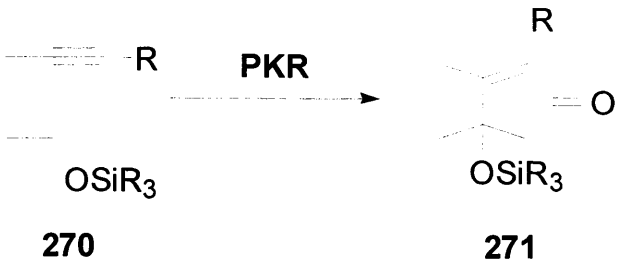
In the case of disubstituted terminal alkene (**327h**, entry 6), impure starting material **327h** was recovered (33%) from the reaction mixture. Trisubstituted alkene (**327i**, entry 7) also did not lead to the desired bicycle. Impure starting material **327i** was recovered (28%) from the reaction mixture.

2.2.7 Conclusion

In conclusion we have shown that silyl ethers derived from allylsilyl chlorides and propargylic alcohols undergo Pauson-Khand reaction, although the substrate scope is currently limited. Yields are low due to purification problems associated with these cycloadducts and it is hoped that removal of silicon tether before any flash column chromatography may lead to easier isolation and enhanced yields of the desired compounds.

2.3 Silyl enol ethers as substrates for the Pauson-Khand reaction

As discussed in the introduction, (section 1.6.2, p. 84), at the start of this project there were no examples in the literature where silyl enol ethers had been used as substrates in an intramolecular Pauson-Khand reaction. We therefore decided to investigate the scope and limitations of using silyl enol ethers of type **270** in the Pauson-Khand reaction (**Scheme 105**). It was hoped that bicycle **271** obtained after the Pauson-Khand reaction could be further transformed and hence may prove useful in the synthesis of various natural products, a model substrate for ingenol **369** in our case.



Scheme 105

2.3.1 Synthesis of substrates

We initially decided to synthesise two substrates, **272a** (terminal alkyne) and **272b** (internal alkyne), to find the optimum reaction conditions for the Pauson-Khand cyclisation of these substrates (**Figure 10**).

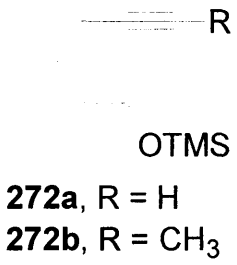


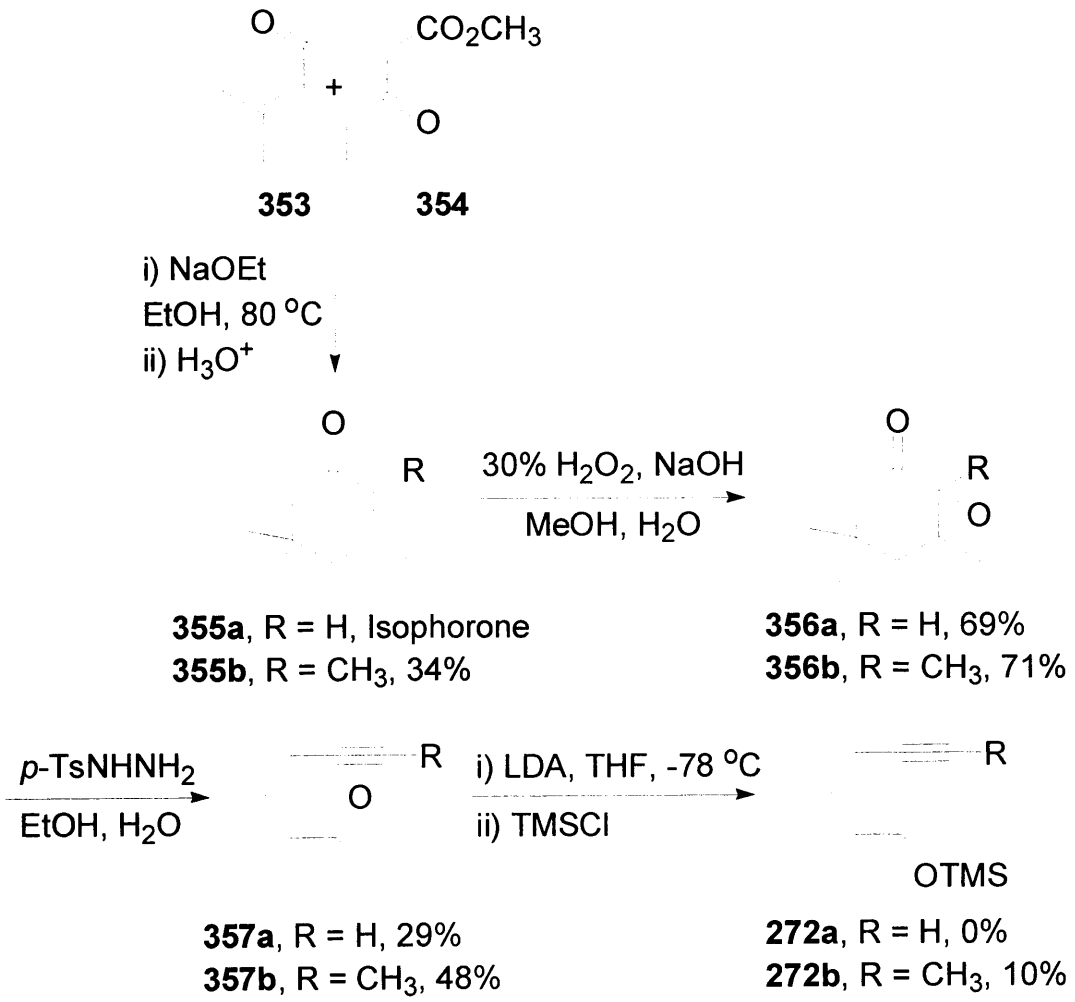
Figure 10

We then hoped to define the scope and limitations of this reaction by synthesising various substrates with different substituents on the alkene and alkyne moieties and subjecting them to the optimised reaction conditions.

Ketones **357a** and **357b** were synthesised, in 29% and 48% yield respectively, by Eschenmoser fragmentation of epoxy ketones **356a** and **356b** using a literature procedure[101] (**Scheme 106**). Epoxy ketones **356a** and **356b** in turn were synthesised from basic epoxidation[102] of isophorone **355a** in the case of **356a** and 2,3,5,5-tetramethylcyclohex-2-en-1-one[103] **355b** in the case of **356b**. Isophorone is commercially available whereas 2,3,5,5-tetramethylcyclohex-2-en-1-one **355b** was synthesised in 34% yield by Robinson annulation of mesityl oxide **353** and methyl-3-oxopentanoate **354** (**Scheme 106**).

We were unable to synthesise either the TMS or TBS enol ether of ketone **357a** using either LDA or KHMDS for the deprotonation of **357a**. Reactions for the synthesis of the TBS enol ether of **357a** showed the presence of both starting ketone and small amounts of the desired silyl enol ether, but we were unable to isolate the desired silyl enol ether from impurities.

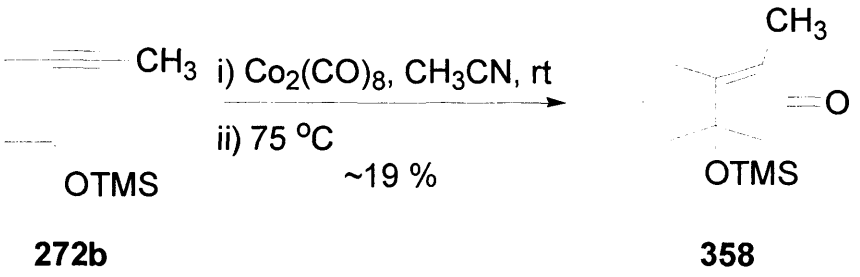
The silyl enol ether **272b** derived from ketone **357b** was synthesised in 10% yield. The low yield was attributed to the volatile nature of this silyl enol ether as well as its hydrolysis to starting ketone **357b** (21% recovery) on silica (**Scheme 106**).



Scheme 106

2.3.2 Pauson-Khand reaction of 272b

The Pauson-Khand reaction of the silyl enol ether **272b** in acetonitrile at 75 °C[91] led to the desired bicyclic cyclopentenone **358** in ~19% yield (**Scheme 107**), however it could not be fully characterised due to the presence of inseparable impurities. ^{1}H NMR and mass spectra showed the isolated compound to be the desired bicycle **358**. This result showed that silyl enol ethers of type **272** would undergo Pauson-Khand cyclisation.

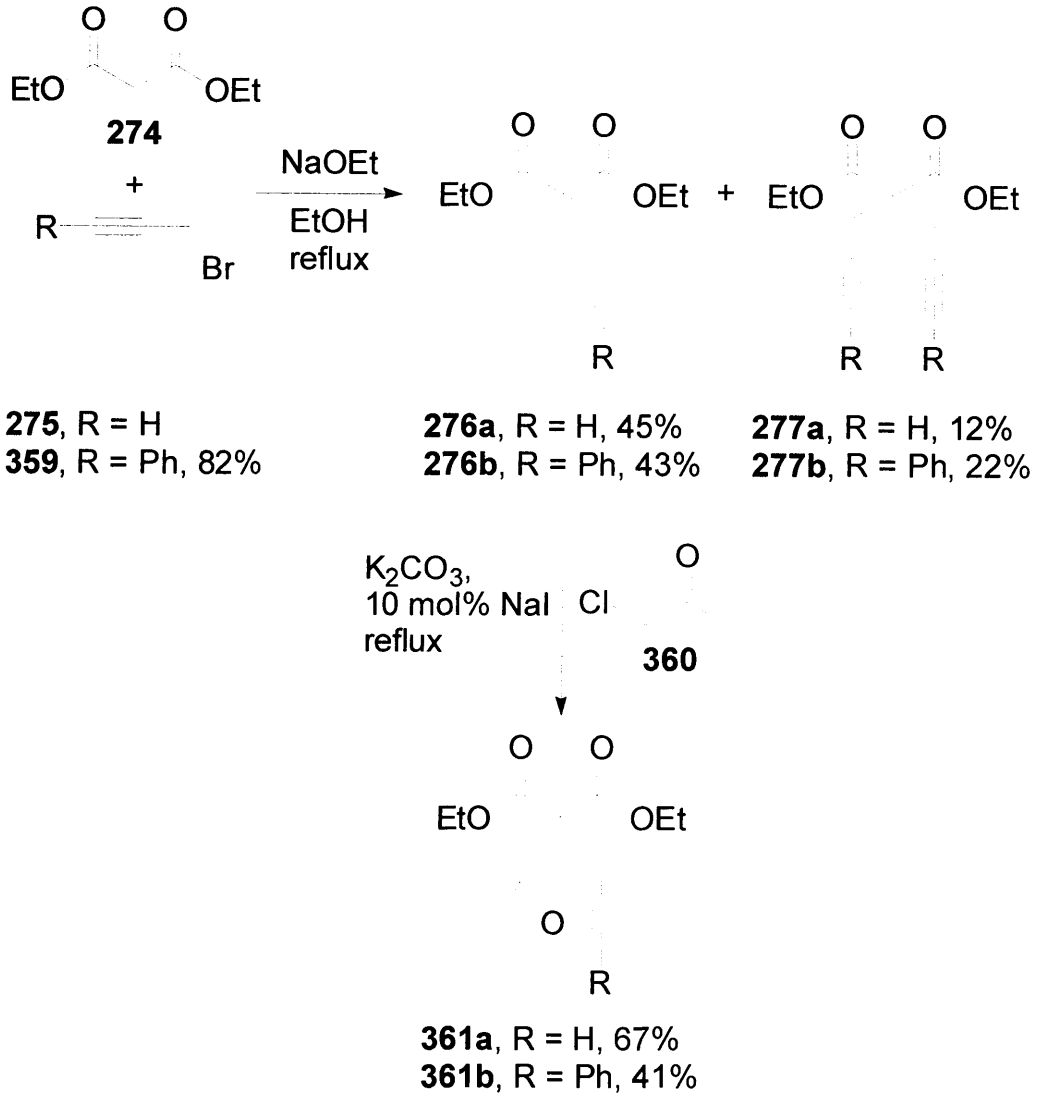


272b **358**

Scheme 107

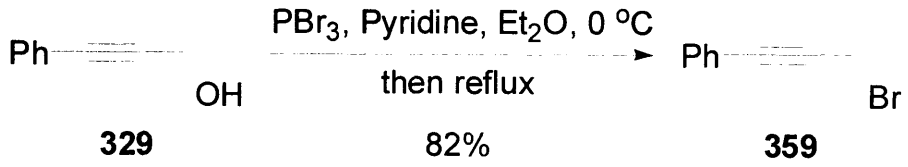
2.3.2 Synthesis of diethyl malonate derivatives

Due to the volatile nature of both **272b** and bicycle **358** and purification difficulties due to the presence of a trimethylsilyl moiety in both **272b** and bicycle **358**, we decided to synthesise diethyl malonate derivatives **361a** and **361b** and to investigate the Pauson-Khand reaction of their silyl enol ethers (**Scheme 108**). We hoped that this series of compounds would prove to be less volatile. The synthesis of two diethyl malonate derivatives **361a** (terminal alkyne) and **361b** (internal alkyne) is illustrated in **Scheme 108**.



Scheme 108

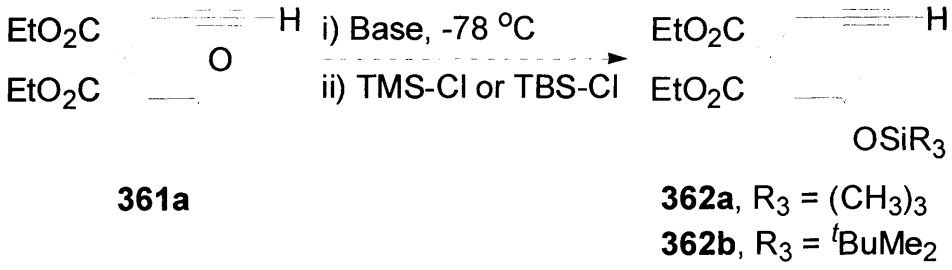
Alkylation of diethyl malonate **274** with the appropriate propargyl bromides **275** and **359** using sodium ethoxide as a base[89] yielded the desired monoalkylated products **276a** and **276b** as well as dialkylated side products **277a** and **277b** (**Scheme 108**). Propargyl bromide **275** is commercially available whereas 1-bromo-3-phenylprop-2-yne[104] **359** was prepared by bromination of 3-phenylprop-2-yn-1-ol **329** as shown in **Scheme 109**. Second alkylation of **276a** and **276b** with chloroacetone **360** using potassium carbonate as a base[90] yielded the two diethyl malonate derivatives **361a** and **361b** required for our studies. Yield of the reaction for the preparation of **361b** was lower than for **361a** due to presence of some unidentifiable and inseparable impurities in **361b**. The purification of **361b** was carried out using a chromatotron ("radial chromatography"), in small batches of 0.20g on silica plates of 4mm thickness.



Scheme 109

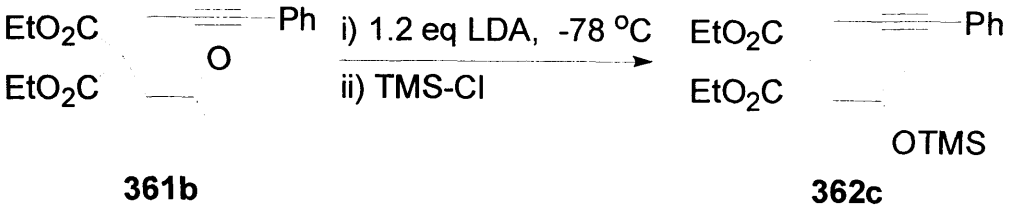
We initially decided to synthesise the trimethylsilyl enol ethers **362a** and **362c** of the two substrates **361a** and **361b** using LDA as a base (**Scheme 110** and **Scheme 111**).

Several attempts to synthesise the trimethylsilyl enol ether **362a** as well as *tert*-butyldimethylsilyl enol (TBS) ether **362b** of the terminal alkyne substrate **361a** using 1.1 equivalents of LDA, KHMDS or LHMDS as bases proved unsuccessful. The reactions either led to recovery of the starting material **361a** along with silyl impurities or unidentifiable product mixtures (**Scheme 110**). We suspected this to be due to the acidity of the terminal alkyne hydrogen (pKa 25) although the ketone hydrogen should be the more acidic (pKa 17-20). The use of 2 equivalents of LDA (to deprotonate both acidic protons) followed by trapping with TBS-Cl again did not lead to isolation of any products.



Scheme 110

We did however successfully synthesise the trimethylsilyl enol ether **362c** as illustrated in **Scheme 111** . The silyl enol ether **362c** was used crude for Pauson-Khand studies as its purification, by flash column chromatography using Florisil® as solid support, led to considerable decomposition to the starting ketone **361b** (46%) and only 26% of the silyl enol ether **362c** was isolated.

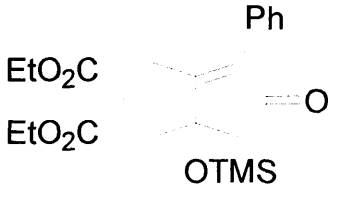


361b **362c**

Scheme 111

2.3.4 Pauson-Khand reaction of Trimethylsilyl ether 362c

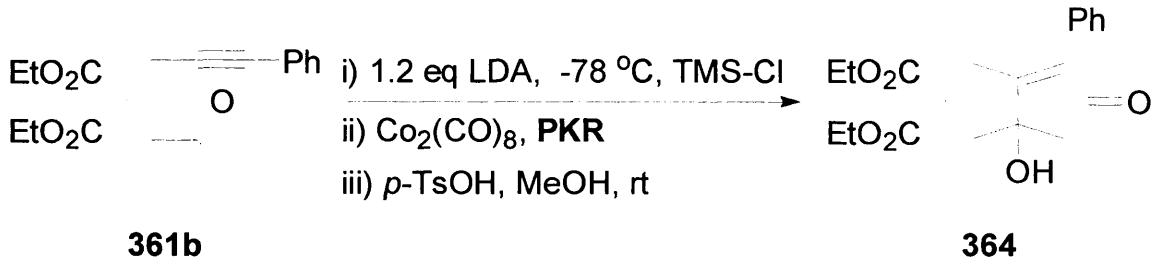
We decided to remove the trimethylsilyl group using *para*-toluenesulfonic acid in methanol after the Pauson-Khand cyclisation due to decomposition of the initial Pauson-Khand product. However ^{1}H NMR spectrum of the isolated compound **363** after the PKR of **362c** promisingly showed some of the AB systems associated with the protons of the two five membered rings (**Figure 11**).



363

Figure 11

The Pauson-Khand reactions were therefore carried out on crude trimethylsilyl enol ether **362c** and the crude Pauson-Khand reaction mixtures were treated with *para*-toluenesulfonic acid to remove the TMS group. The results for the Pauson-Khand cyclisation of the trimethysilyl enol ether **362c** to yield 4-hydroxy cyclopentenone **364** under various Pauson-Khand reaction conditions are summarised in **Table 25** for **Scheme 112.**



361b **364**

Scheme 112

Table 25. Pauson-Khand reactions of 361b

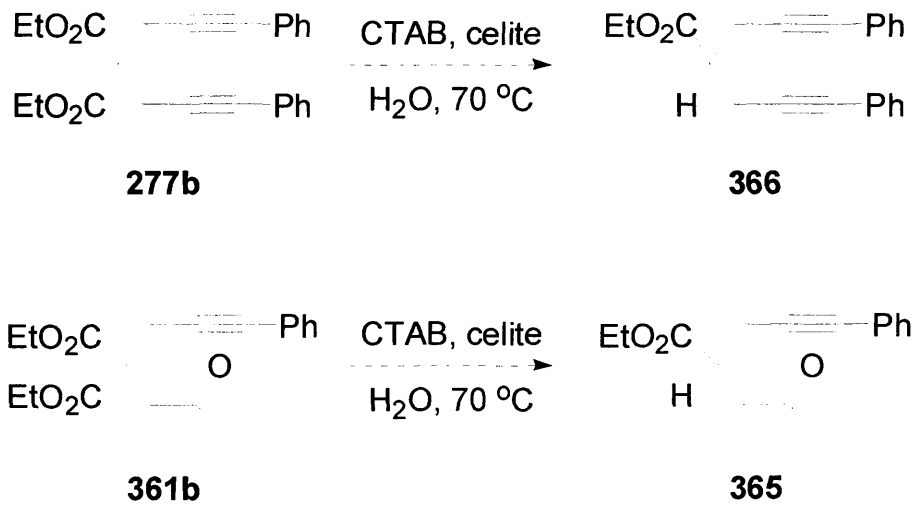
Entry	PKR conditions	Yield (%)	Comments
1	Toluene, reflux	29	
2	CH_3CN, 75 °C[91]	23	**361b** (24%) contaminated with cobalt impurities
3	*n*-BuSMe, 1,2-DCE, 83 °C[29]	24	**361b** (41%)
4	Toluene, 4Å MS, reflux[34]	0	Inseparable product mixtures
5	NMO, CH_2Cl_2, rt[25]	0	**361b** (23%) contaminated with cobalt impurities
6	$CyNH_2$, 1,2-DCE, 83 °C[28]	0	**361b** (59%)
7	H_2O, CTAB, Celite, 70 °C[35]	0	Monoester **365** (7%) along with unclean **361b**

As can be seen from **Table 25**, 4-hydroxy cyclopentenone **364** was obtained under only three of the reaction conditions tested (entries 1, 2 & 3). The highest yield of bicycle **364** (29% over 3 steps) was obtained when the reaction was carried out in toluene (entry 1). The starting ketone **361b** was recovered in most cases. An interesting reaction occurred when the Pauson-Khand reaction was carried out in aqueous medium[35] (entry 7). Along with some unclean starting ketone **361b**, monoester **365** was also isolated in 7% yield (**Figure 12**).

365

Figure 12

This was peculiar as generally decarboethoxylation of β-ketoesters requires forcing reaction conditions such as LiCl in refluxing DMSO (Krapcho decarboxylation[105]). In order to see whether the presence of cobalt was necessary for this decarboethoxylation to occur we carried out two test reactions in the absence of $Co_2(CO)_8$ as illustrated in **Scheme 113** below.

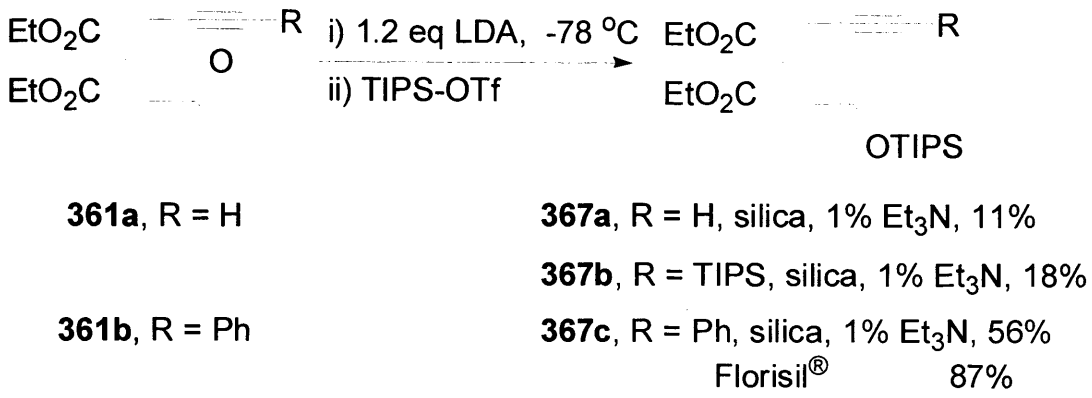


Scheme 113

In both cases 100% recovery of starting materials was observed leading to the conclusion that presence of $Co_2(CO)_8$ was necessary for this unusual reaction to occur.

2.3.5 Synthesis and Pauson-Khand reaction of Triisopropylsilyl ethers

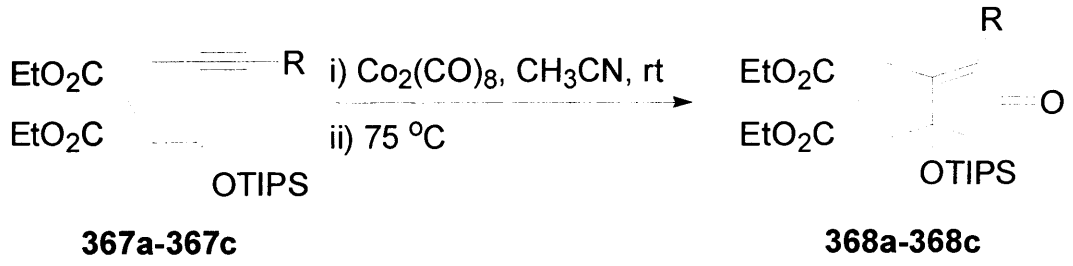
In order to establish whether the sterically bulky silyl enol ethers such as TIPS enol ethers would also undergo Pauson-Khand reaction we decided to synthesise TIPS enol ethers of **361a** and **361b** as illustrated in **Scheme 114**.



Scheme 114

During the synthesis of **367a**, **367b** was also isolated in 18% yield along with the starting material **361a** (26%). This showed that the terminal alkyne hydrogen was also being deprotonated along with the ketone hydrogen. TIPS enol ether **367c** could be purified on silica, however a higher yield of 87% was obtained when Florisil® was used as solid support. This is most likely due to the hydrolysis of the enol ether **367c** occurring on silica.

The results of the Pauson-Khand reaction of TIPS enol ethers in acetonitrile[91] (**367a**, **367b** and **367c**) are illustrated in the **Scheme 115**, and **Table 26**.



Scheme 115

Table 26. PKR of TIPS enol ethers

Entry	Substrate	Yield (%)	Comments
1	**367a** (R = H)	0	Unidentifiable products
2	**367b** (R = TIPS)	0	**367b** recovered (84%)
3	**367c** (R = Ph)	13	**367c** recovered (65%)

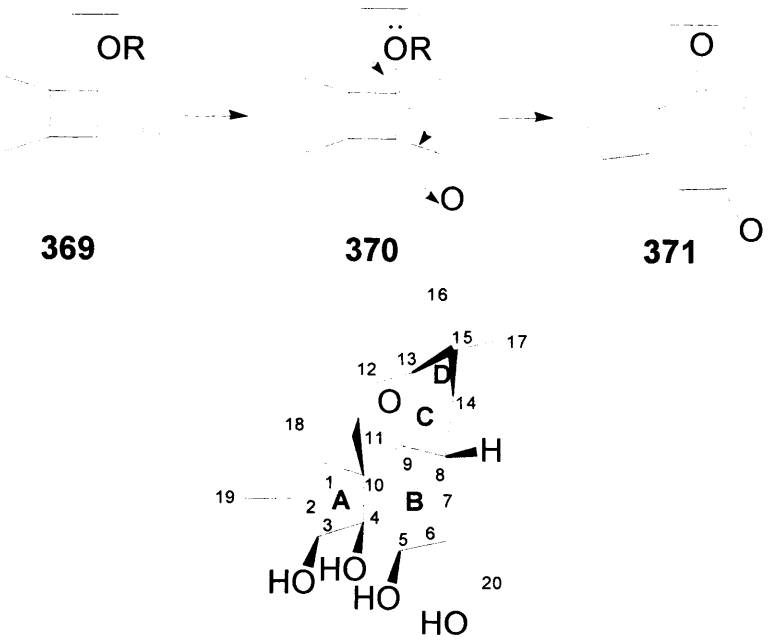
In the case of terminal alkyne (**367a**, entry 1) unidentifiable product mixtures were obtained whereas PKR of **367b** (entry 2) led to 84% recovery of the starting TIPS enol ether **367b**. Only **367c** led to the desired bicycle **368c**, in 13% yield along with 65% recovery of the starting TIPS enol ether **367c**. Incomplete complexation of all three substrates (**367a-367c**) with dicobalt octacarbonyl was observed.

2.3.7 Conclusion

The TMS enol ether of the internal alkyne substrate **362c** undergoes Pauson-Khand reaction in moderate yields, however the TIPS enol ether **367c** of the same substrate undergoes the cyclisation reaction in poor yield (13%). **367c** was also recovered in 65% yield. The TIPS enol ethers of the terminal alkyne substrate **367a** and **367b** do not undergo Pauson-Khand reaction.

2.4 Model substrate for the synthesis of ingenol

We decided to apply the silyl enol ether methodology to a model substrate **369** for synthesis of compound **371** containing A, B and C rings of ingenol **372** (**Scheme 116**). Pauson-Khand reaction of the model substrate **369** would lead to the installation of B and C rings of ingenol in one step.



Ingenol

372

Scheme 116

2.4.1 Origin, Biological activity and mode of action of ingenol

Ingenol[106] **372** is a highly oxygenated tetracyclic diterpene, isolated initially from the *Euphorbia ingens* species of the *Euphorbiaceae* plant family, by the Hecker group in 1968. Diverse ingenane types with different oxidation states at C-3, C-4, C-5, C-12, C-13, C-16 or C-20 have also been isolated.[107] It has attracted considerable interest from both the chemical and biological communities because of its unique structure and an array of biological properties.

The identification of cellular signalling systems and the design and synthesis of small molecules that regulate these systems is at the forefront of modern drug design[108]. Protein Kinase C is a central mediator of cellular signal transduction for a large class of hormones and cellular effectors that generate the lipophilic secondary messenger 1,2-diacylglycerol **373**, *e.g.,* through activation of phosphatidylinositol 4,5-bis(phosphate) turnover. Various esters of ingenol are able to substitute for 1,2-diacylglycerol **373**, the endogenous activator of PKC. In addition to ingenol **372**, several other natural products

including teleocidin **374**, esters of phorbol **375** and asplysiatoxin **376** mimic the function of diacylglycerol **373** (**Figure 13**). Although several proposals for a pharmacophore common to these structurally dissimilar activators of PKC have been described, a conclusive structure-activity relationship has not been established. The synthesis and study of specifically modified analogues of these natural product leads should establish the structural requirements for the activation of PKC that are common to these dissimilar substances and ultimately lead to the development of new therapeutic drugs for the treatment of inflammatory and proliferative diseases.[107]

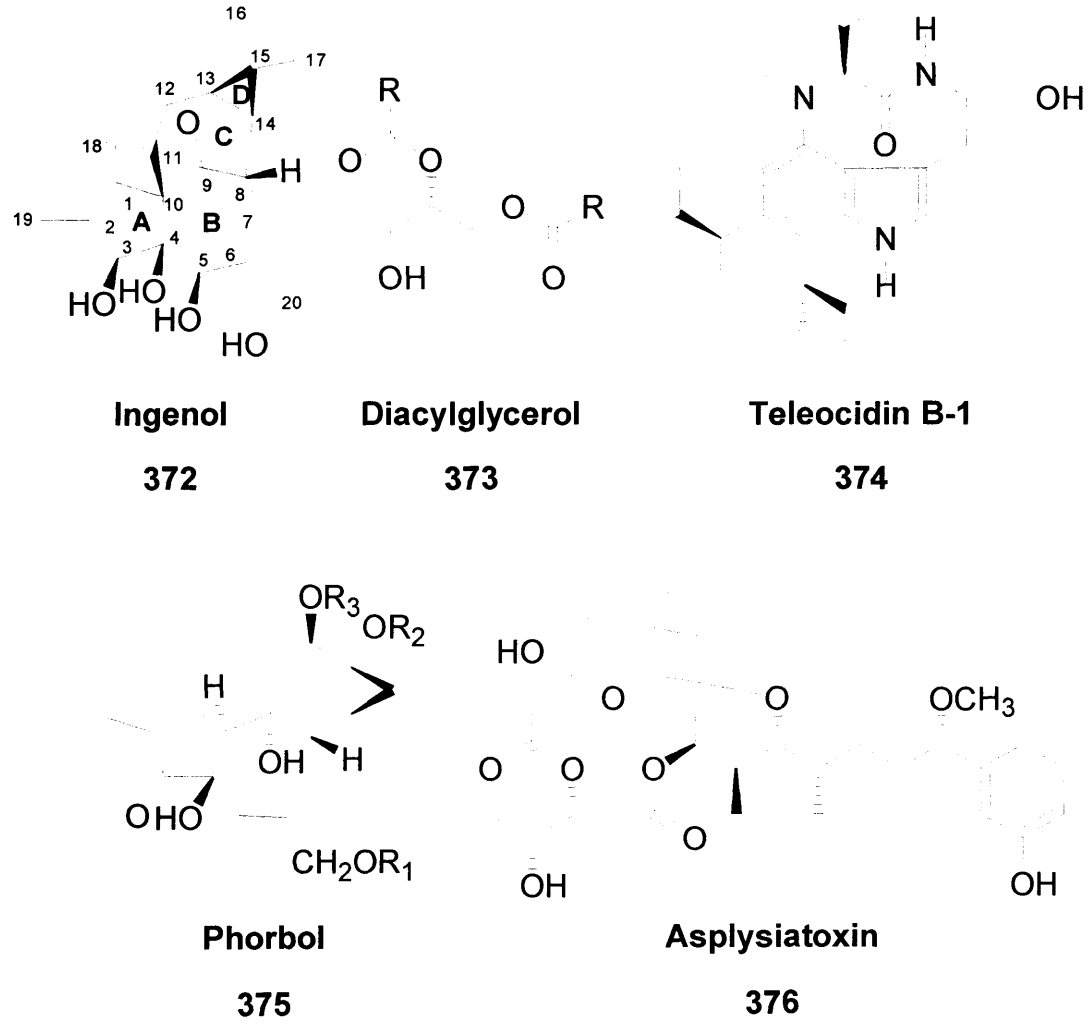


Figure 13

Ingenol esters were initially reported to be potent tumour promoters.[106] Since then, numerous ingenol derivatives have been identified as tumour-promoting activators of

PKC.[109,110] Paradoxically, as long ago as 1976, there have been reports of ingenol derivatives having antitumour such as antileukemic properties as well.[111,112]

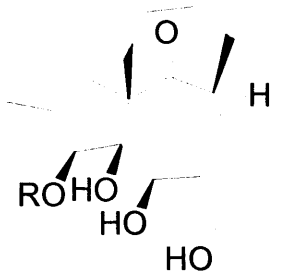
In several studies on the biological properties of ingenoids there have been clear separations between tumour-promotion and potentially therapeutic activities, suggesting that there may be a mechanistic pathway independent of PKC activation responsible for biological activity.[113,114] The evaluation of antitumour activity and PKC activation of C-20 modified analogues of ingenol has shown that chemical manipulation can effectively dissect cytotoxicity and tumour-promoting activity of ingenoids.[115]

Recently ingenol derivatives have been shown to affect HIV-1 replication. In acutely infected cells, ingenol derivatives were shown to be powerful inhibitors of viral adsorption to the host cell, greatly inhibiting viral replication.[116]

An efficient synthetic route to ingenol will allow access to novel ingenoid analogues and their SAR studies will give insight into the detailed mechanism of activity of the ingenol esters, and possibly lead to new therapeutic treatments.

2.4.2 Inside-outside stereochemistry of ingenol

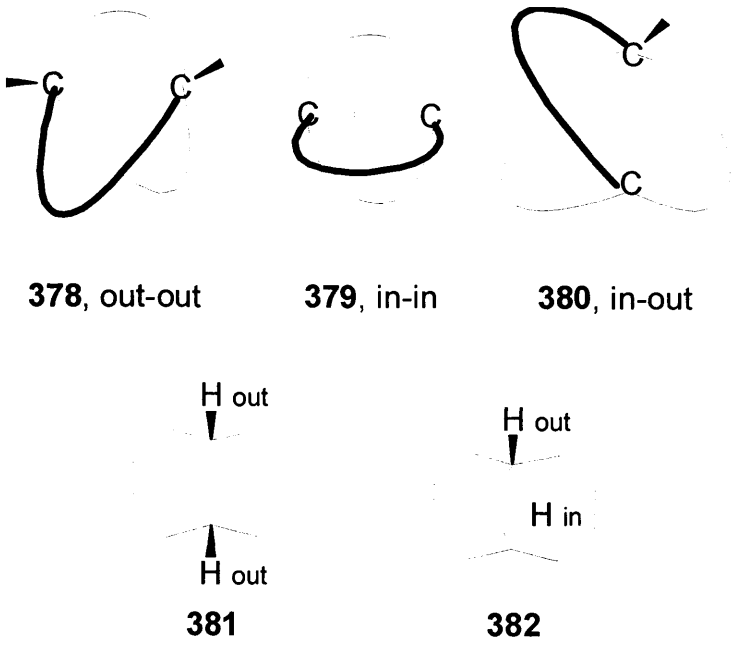
Ingenol **372** is a highly oxygenated tetracyclic diterpene possessing a bicyclo[4.4.1]undecane skeleton in BC rings. While the high degree of oxygenation, notably the *cis*-triol (from C-3 to C-5 on the β face of A and B rings), represents an important challenge to the synthesis, the most imposing obstacle to the synthesis of ingenol is the establishment of highly strained 'inside-outside' or *trans* intrabridgehead stereochemistry of the B, C ring system. This unique stereochemical feature appears to play a very important role in the biological properties of the ingenanes, as Paquette[117] has reported that a highly functionalised ingenane analogue **377**, (**Figure 14**), which has a *cis* rather than *trans* intrabridgehead stereochemistry (the C-8 epimer of ingenol), possessing the fully functionalised A and B rings of ingenol, is completely devoid of biological activity.



377, R = $C_{15}H_{31}CO$

Figure 14

Bridged bicyclic systems can exist as three different stereoisomers[118]: an out-out isomer **378**, an in-in isomer **379** and an in-out isomer **380** (**Figure 15**). Usually the in-in isomer **379** is most unstable because of the severe repulsive interaction between the inside atoms. However, the energy difference between in-out and out-out isomers varies depending on the system. In the ingenane ring system, the in-out isomer is generally more strained than the out-out isomer.[119] According to MM2 calculations, in-out bicyclo[4.4.1]undecane **382** is more strained than its out-out isomer **381** by 6.3 kcal mol^{-1}, whereas the analogous out-out and in-out bicyclo[4.4.1]undecan-7-one configurations (substructure present in ingenol) differ in strain energy by 3.3 kcal mol^{-1}. Ingenol itself is more strained than its out-out isomer (isoingenol) by 5.9 kcal mol^{-1}.[119]



378, out-out **379**, in-in **380**, in-out

381 **382**

Figure 15

Total synthesis of ingenol has proved very challenging because of this highly strained C-8/C-10 *trans* intrabridgehead system and has stimulated the interest of many synthetic organic chemists.

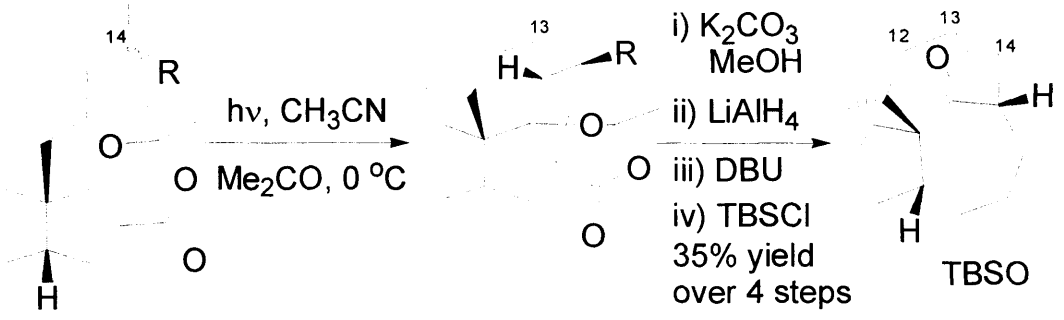
2.4.3 Previous syntheses of ingenol

Although several groups have been working towards the total synthesis of ingenol since the early 1980s, the first total synthesis of ingenol was reported by Winkler in 2002[120]. Since then two other total syntheses, first by Kuwajima in 2003[121] and second by Wood in 2004[122] have been reported. One formal synthesis of ingenol was also reported by Kigoshi in 2004[123].

2.4.3.1 Winkler's first total synthesis of Ingenol[120]

The total synthesis of (±)ingenol proceeded in 43 steps with an 80% average yield per step. Winkler and coworkers[120] employed an intramolecular dioxenone photoaddition-fragmentation approach to set up the *trans* intrabridgehead stereochemistry of C-8/C-10 of ingenol.

Irradiation of dioxeneone substrate **383** led to the desired photoadduct **384** in low (16%) yield, however photocycloadddition of the allylic chloride **385** derived from **383** proceeded in 60% yield to give desired photoadduct **386** (**Scheme 117**). Fragmentation of **386** with methanolic potassium carbonate, followed by LAH reduction of the derived ester, elimination of the chloride and silylation of the primary alcohol gave **387** as a 7:1 ratio of C-6 α:β epimers in 35 % yield over four steps. This compound **387**, with desired C-8/C-10 in-out stereochemistry, was further transformed into (±)-ingenol over several steps.



383, R = OH
385, R = Cl

384, R = OH, 16%
386, R = Cl, 60%

387

Scheme 117

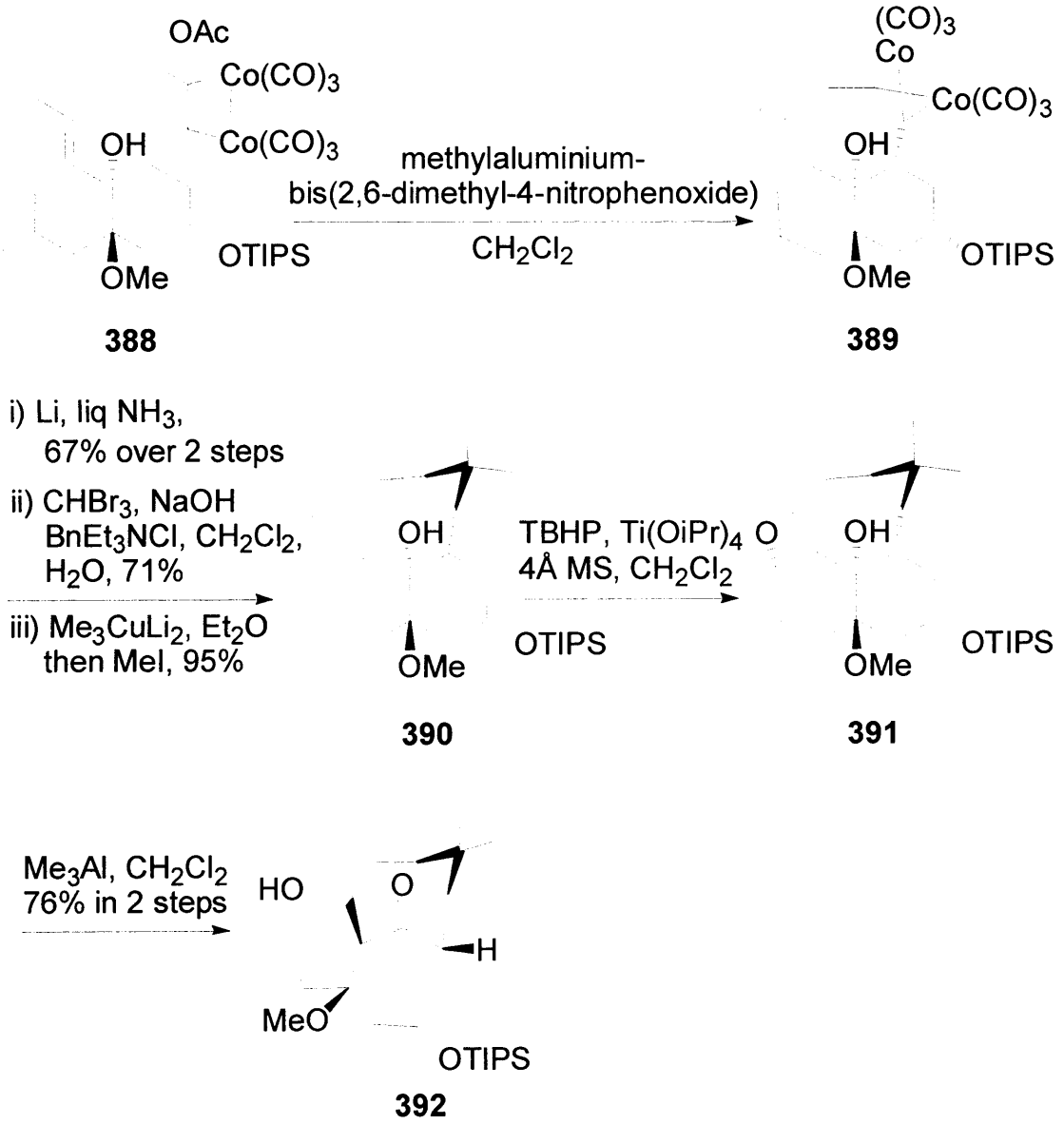
2.4.3.2 Kuwajima's total synthesis of Ingenol[121]

Kuwajima and coworkers carried out the total synthesis of (±)-ingenol in 45 steps in approximately 0.1 % overall yield[121].

They employed a novel intramolecular cyclisation reaction of acetylene dicobalt complex **388** and a rearrangement reaction of epoxy alcohol **391** for constructing the ingenane skeleton.

Cobalt complex **388**, under the influence of methylaluminium bis(2,6-dimethyl-4-nitrophenoxide), underwent a cyclisation reaction to afford allyl alcohol **389** containing the C(11) α-methyl group. The dicobalt acetylene complex moiety of **389** was used for stereoselective construction of the D ring through Birch reduction,

dibromocyclopropanation, and methylation. Transformation of the tetracyclic carbon framework into an ingenane skeleton was achieved via stereoselective epoxidation of allyl alcohol **390** followed by treatment with trimethylaluminium to set up the *trans* intrabridgehead C-8/C-10 stereochemistry of ingenol, as illustrated in **Scheme 118**. **392** was converted to (±)-ingenol over several steps.

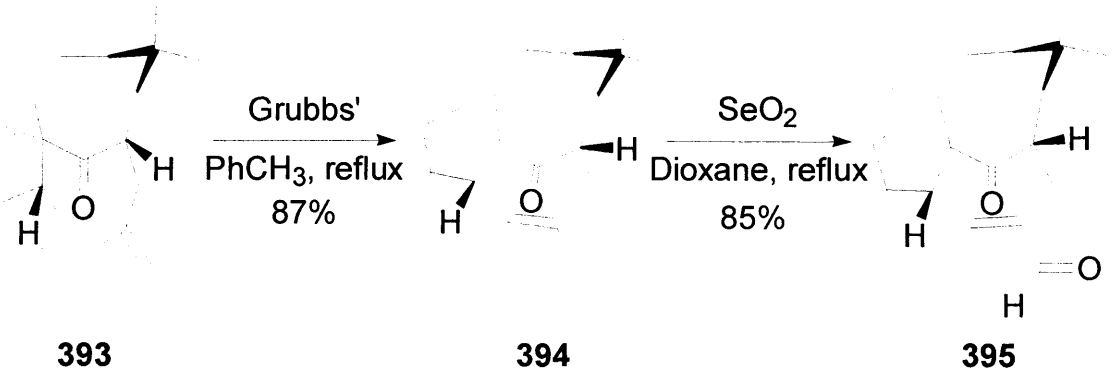


Scheme 118

2.4.3.3 Kigoshi's formal total synthesis of Ingenol[123]

Kigoshi and coworkers[123] have developed a direct cyclisation method for the construction of highly strained skeleton of ingenol via ring closing olefin metathesis.

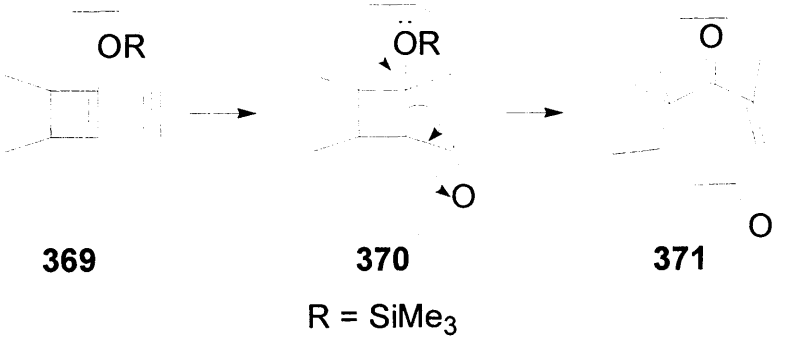
The compound **394**, obtained after the ring closing metathesis reaction of **393**, was further elaborated to Winkler's aldehyde[120] **395**, a key intermediate in Winkler's total synthesis of ingenol.



Scheme 119

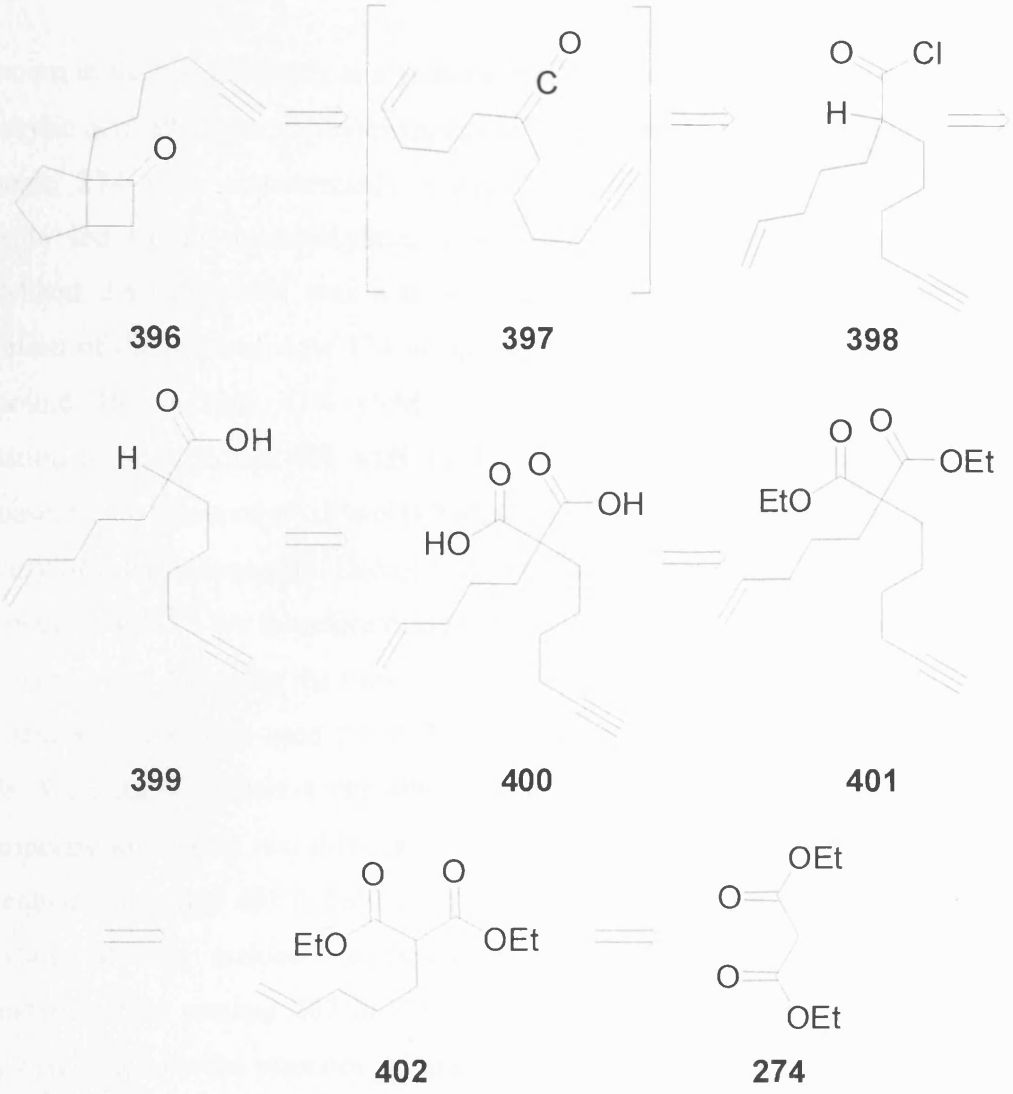
2.4.4 Retrosynthetic analysis of our model substrate

We decided to investigate the synthetic utility of the Pauson-Khand reaction of a silyl enol ether **369**, for synthesis of the ingenane skeleton. We hoped that the Pauson-Khand reaction of key intermediate **369** would form the tetracyclic compound **370**, which would undergo retro aldol reaction to relieve ring strain and therefore lead to compound **371** containing the ingenane ring skeleton (**Scheme 120**).



Scheme 120

Silyl enol ether **369** will be synthesised from cyclobutanone **396**. **Scheme 121** below shows retrosynthetic analysis of the key intermediate **396**.

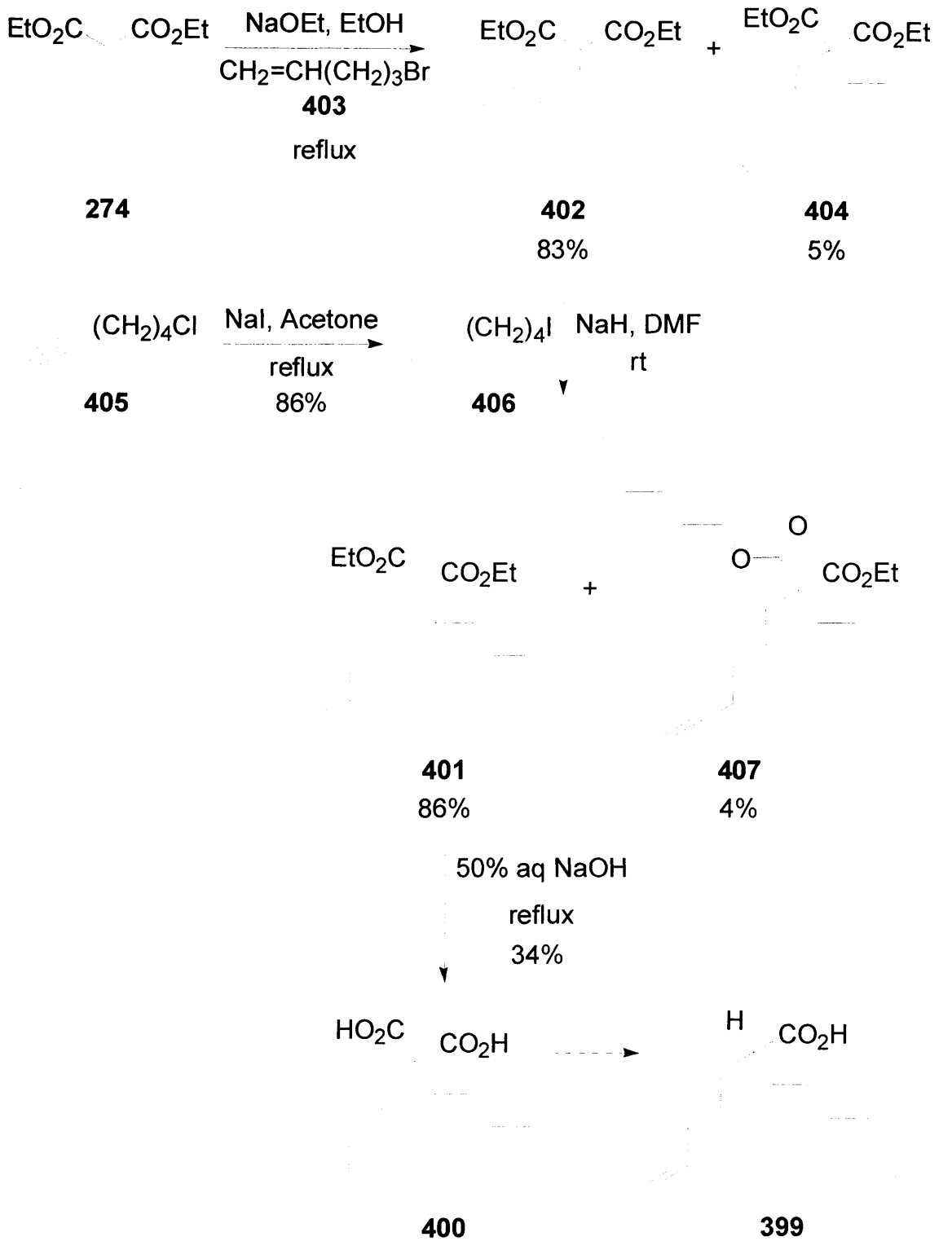


Scheme 121

Cyclobutanone **396** will be synthesised from [2+2] cycloaddition of ketene **397** generated *in situ* from acid chloride **398**. Monocarboxylic acid **399** will be synthesised by decarboxylation of dicarboxylic acid **400** which in turn will be generated from ester hydrolysis of diethyl malonate derivative **401**. Dialkylation of diethyl malonate, first with 5-bromopent-1-ene and then alkylation of derivative **402** with 6-chlorohex-1-yne will lead to diethyl dialkylmalonate derivative **401**. Synthesis of silyl enol ether from cyclobutanone **396** will yield model substrate for the synthesis of ingenol skeleton.

2.4.5 Synthesis of Cyclobutanone 396

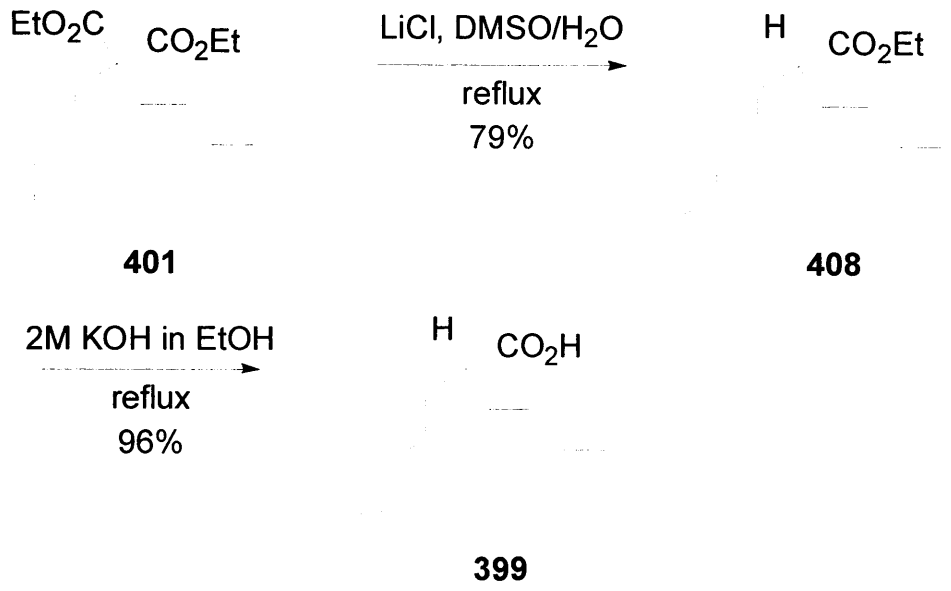
As shown in the retrosynthetic analysis, we initially decided to carry out the synthesis of carboxylic acid **399** from diethyl malonate **274** (**Scheme 122**). The alkylation of diethyl malonate **274** with commercially available 5-bromopent-1-ene **403** using sodium ethoxide led to the monoalkylated malonate derivative **402** in 83% yield.[89] The dialkylated derivative **404** was also obtained in 5% yield. Carrying out this initial alkylation of diethyl malonate **274** using NaH, as a base, in THF,[124] led to the desired compound **402** in only 43% yield. We initially decided to carry out the second alkylation of intermediate **402** with 6-chlorohex-1-yne **405** using potassium carbonate as a base, in the presence of 10 mol% NaI, in acetone.[90] However this reaction led to the recovery of intermediate **402**. Use of NaH as a base in THF also led to the recovery of intermediate **402**.[123] We therefore decided to synthesise 6-iodohex-1-yne[125] **406** from 6-chlorohex-1-yne **405** using the Finkelstein reaction conditions (NaI in acetone, reflux). This reaction is widely used for S_N2 displacement of one alkyl halide with another halide. With the 6-iodohex-1-yne **406** in hand, we carried out the second alkylation of intermediate **402** using two different bases. Use of sodium ethoxide as a base yielded the desired compound **401** in 58% yield whereas use of NaH in DMF led to the desired dialkylated diethyl malonate derivative **401** in 86% yield along with the minor transesterification product **407** in 4% yield. The transesterification product **407**, most likely originated by the presence of small amounts of moisture in the reaction mixture which led to the hydrolysis of the iodide **406** to the corresponding alcohol. This in turn reacted with one of the diethyl malonate esters of **401**. The hydrolysis of **401** using 50% aqueous NaOH solution[126] led to the diacid **400** in a disappointingly low yield of 34%, most likely due to its solubility in aqueous phase and hence reduced extraction into the organic phase. We then attempted the decarboxylation of the diacid **400** using 3 different reaction conditions including (i) heating a solution of the diacid **400** in 6 M H_2SO_4,[127] (ii) heating the diacid **400** neat without any solvent[128] and (iii) heating a solution of the diacid **400** in toluene. None of these conditions led to the desired monoacid **399** and unidentifiable reaction mixtures were obtained.



Scheme 122

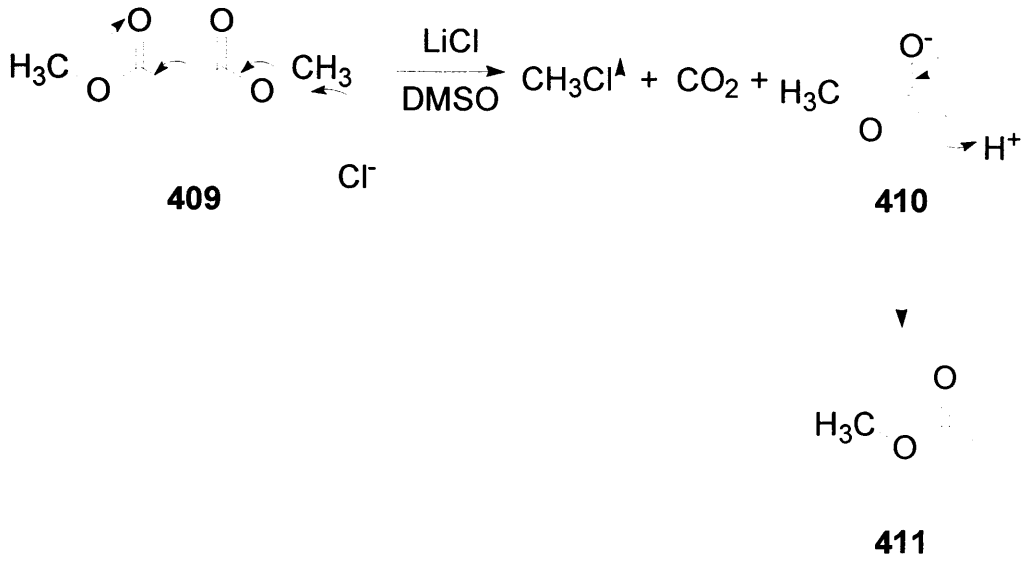
Due to the low yield of diacid **400** and failure to cause its decarboxylation led to a revised synthesis of monoacid **399**, as illustrated in **Scheme 123**. We decided to use Krapcho reaction conditions[105] (LiCl, DMSO, reflux) for decarboethoxylation of diester

401 to synthesise the monoester **408** in 79% yield. The basic hydrolysis[129] of this monoester **408** led to the desired monoacid **399** in 96% yield (**Scheme 123**).



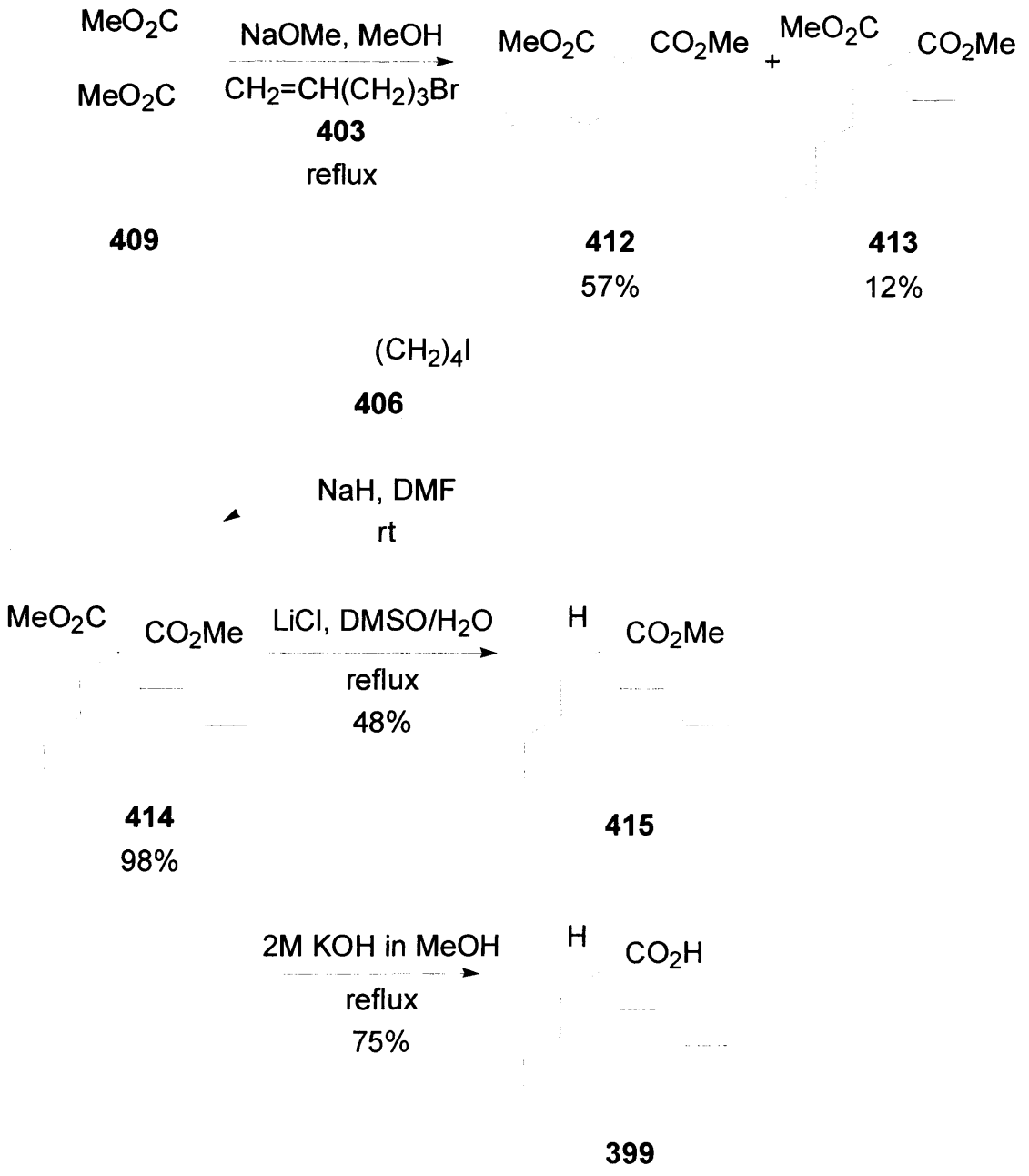
Scheme 123

Initially we carried out the Krapcho reaction, to synthesise monoester **408**, at 300–500 mg scale and the yields were low (ranging from 47%-53%). However the yield of the reaction improved when carried out on larger scale of 2.3 g leading to 79% yield of the desired monoester **408**. Since Krapcho reaction takes place by the nucleophilic attack of the chloride ion on the carbon of the ester (as illustrated in **Scheme 124**), we hoped that the yield of this reaction would improve further when carried out on analogous dimethyl malonate derivative compared to the diethyl malonate derivative **401** since OCH_3 is less sterically hindered than OCH_2CH_3 and therefore nucleophilic attack of Cl^- ion would be facilitated.



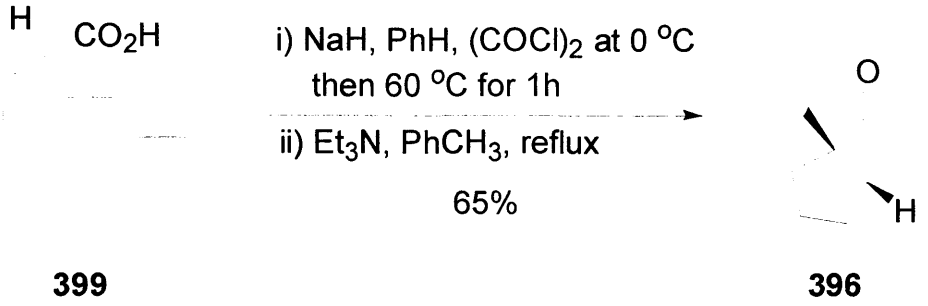
Scheme 124

The dimethyl malonate derivative **414** was synthesised using the same sequence of steps and procedures as for diethyl malonate derivative **401** and is illustrated in **Scheme 125**. As can be seen from **Scheme 125**, (i) yield of monoalkylated dimethyl malonate derivative **412** decreased considerably (57%) compared to its diethyl malonate analogue (83%), (ii) transesterification product was not obtained after the second alkylation and (iii) most importantly the yield of the Krapcho reaction did not increase as expected, instead mono ester **415** was obtained in only 48% yield compared to its ethyl analogue **408** which was obtained in 79% yield. We therefore decided to use the diethyl malonate derivatives for our studies. The basic hydrolysis of the monoester **415** led to the monoacid **399** in 75% yield.



Scheme 125

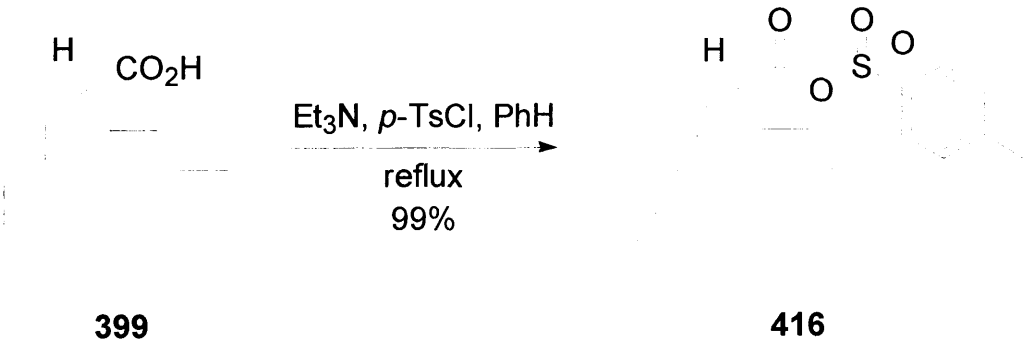
Cyclobutanone **396** was obtained, in 65% yield, by the synthesis of acid chloride from monoacid **399** and then by *in situ* generation of ketene, using triethylamine as a base, which underwent [2+2] cycloaddition (**Scheme 126**).[130]



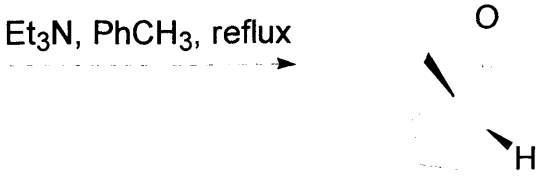
399 **396**

Scheme 126

The synthesis of cyclobutanone **396** was also attempted using the route shown in **Scheme 127** via the tosylate **416**.[131] The tosylate **416** could be purified by flash column chromatography, however it did not lead to the generation of cyclobutanone **396**. ^{1}H NMR spectra of the fractions obtained after flash column chromatography showed alkene protons as well as protons of the tosylate, indicating that the ketene was not formed during the reaction.



399 **416**

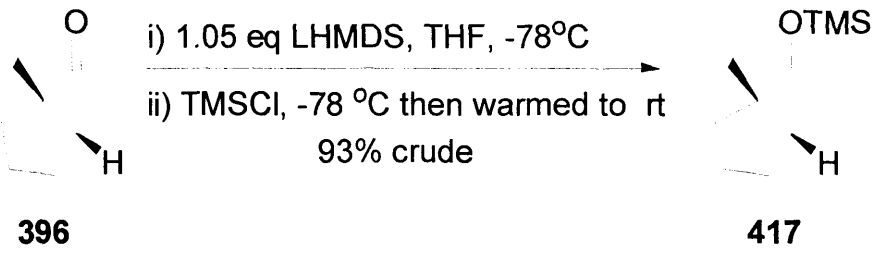


396

Scheme 127

2.4.6 Synthesis and Pauson-Khand reaction of trimethylsilyl enol ether 417

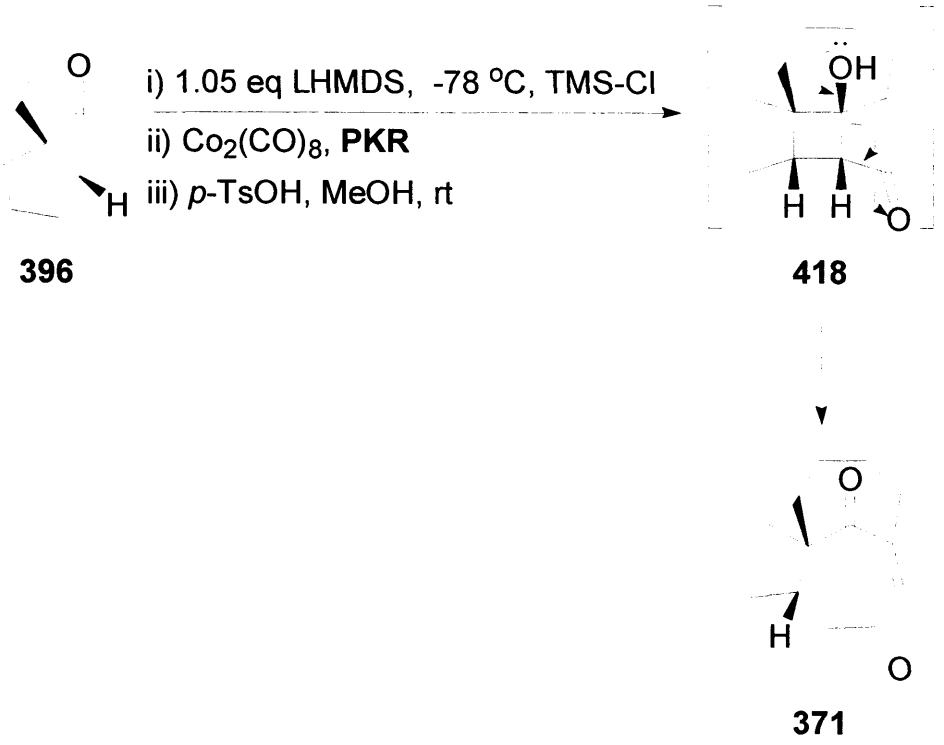
We decided to study the Pauson-Khand reaction of trimethylsilyl enol ether **417**, generated from cyclobutanone **396**. Trimethylsilyl enol ether was chosen as in our previous methodology studies, (section 2.3.4, p. 128), TMS enol ethers led to the best results for Pauson-Khand cyclisations. The silyl enol ether **417** was generated from cyclobutanone **396** using LHMDS as a base[132] (**Scheme 128**). ^{1}H NMR spectrum of the crude **417** showed it to be clean containing only minor trimethylsilyl impurities.



396 **417**

Scheme 128

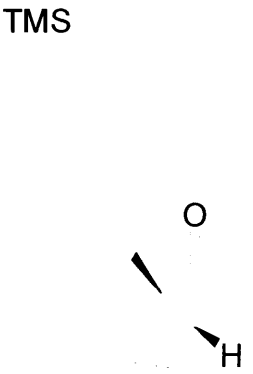
Again as in the case of substrate **361b**, (section 2.3.4, p. 128), we decided to use the TMS enol ether **417** crude for our Pauson-Khand studies due to the purification problems associated with the TMS moiety. This group was also removed using *para*-toluenesulfonic acid before any flash column chromatography was carried out on Pauson-Khand reaction mixtures. It was hoped that after the removal of the TMS group, the Pauson-Khand adduct **418** would spontaneously undergo retro-aldol reaction in order to relieve ring strain and hence lead to the formation of the desired compound **371**, containing the A, B and C rings of ingenol (**Scheme 129**).



396 418 371

Scheme 129

The Pauson-Khand reaction of **417** mediated by *n*-butyl methyl sulfide[29] generated a complex reaction mixture containing various unidentifiable compounds. **419** was the only compound identified and characterised after flash column chromatography and was obtained in 5% yield (from cyclobutanone **396**). Surprisingly, transfer of the TMS moiety onto the terminal alkyne was observed (**Figure 16**).



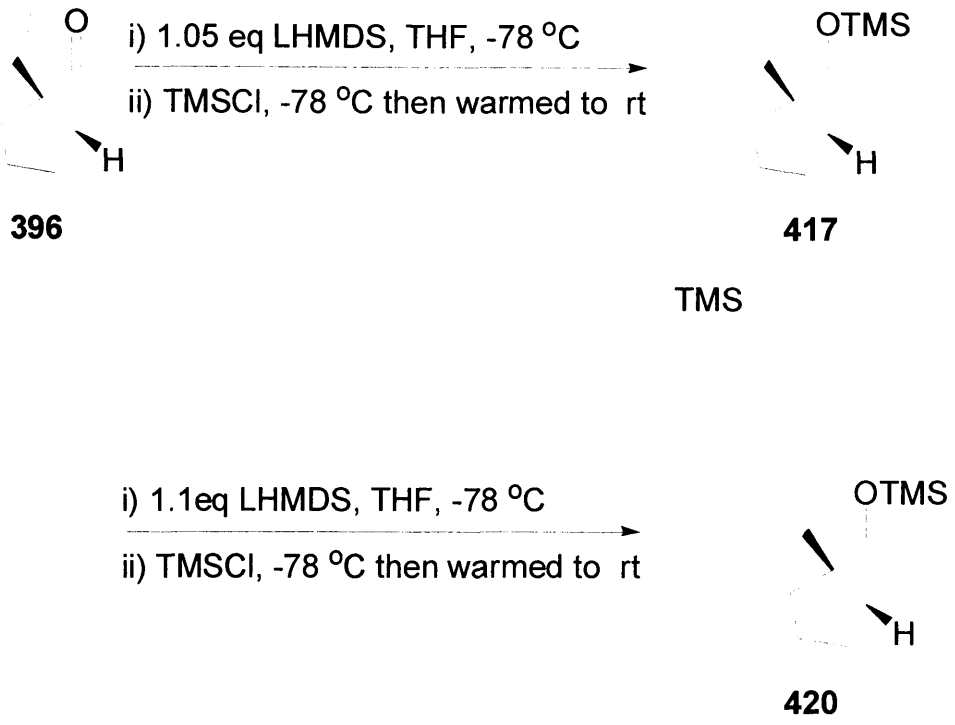
419

Figure 16

The Pauson-Khand reaction of **417** in acetonitrile[91] at reflux also led to complex and unidentifiable reaction mixtures. During the synthesis of the dicobalt hexacarbonyl complex of **417**, acetonitrile appeared to be forming a complex with dicobalt octacarbonyl ($Co_2(CO)_8$), as addition of dry acetonitrile to $Co_2(CO)_8$ led to release of gas bubbles, presumably carbon monoxide and change of the colour of the solution from orange brown to deep red was also observed. Therefore the dicobalt hexacarbonyl complex of silyl enol ether **417** was not being formed and hence Pauson-Khand reaction was not taking place. In that case we would expect to isolate cyclobutanone **396** after the acidic workup, however none was isolated. The Pauson-Khand reaction of **417** in toluene at reflux also generated complex and unidentifiable reaction mixtures. Some cyclobutanone **396**, contaminated with unidentifiable impurities, was recovered in 31% crude yield.

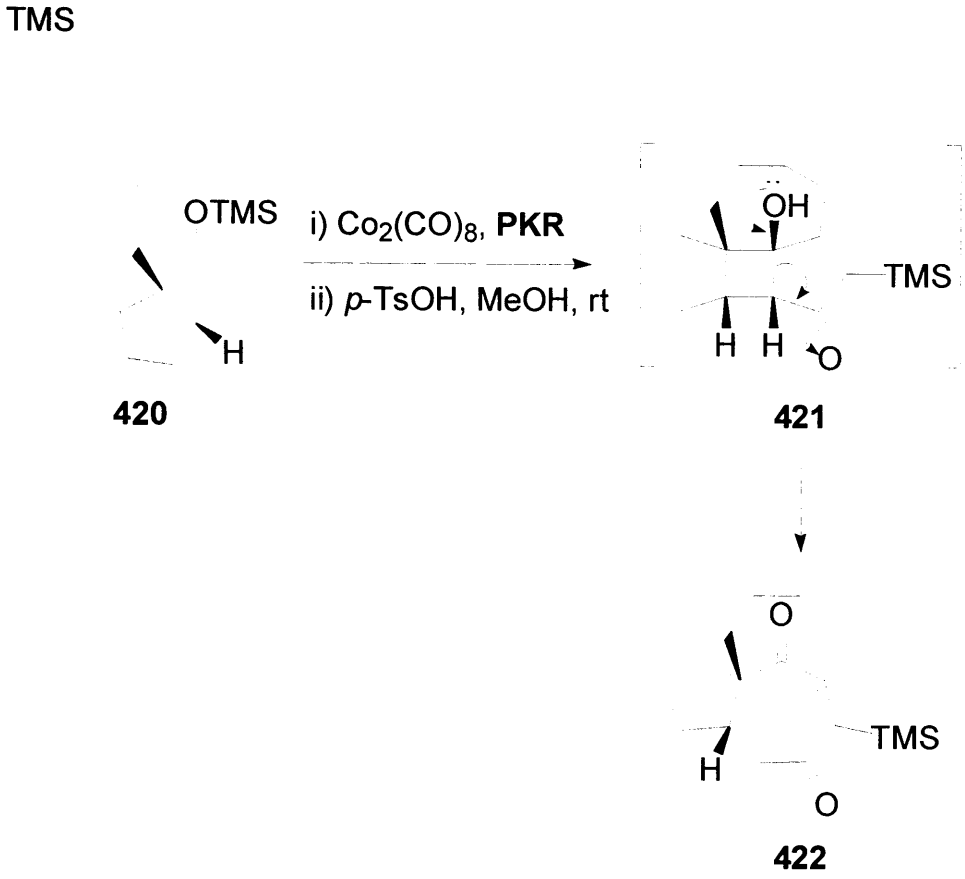
2.4.7 Synthesis and Pauson-Khand reaction of trimethylsilyl enol ether 420

Along with the terminal alkyne trimethylsilyl enol ether **417** we decided to synthesise the TMS enol ether **420** to study the effect of substitution at the alkyne position. **420** was easily synthesised in 2 steps from cyclobutanone **396** as illustrated in **Scheme 130** using LHMDS as a base.[132]



Scheme 130

First deprotonation with LHMDS followed by capturing of the enolate with trimethylchlorosilane led to **417**. Use of 1.1 equivalent of LHMDS deprotonated the terminal alkyne which was then silylated using trimethylchlorosilane. This sequence of steps led to trimethylsilyl enol ether **420**. ^{1}H NMR spectrum of the crude **420** showed it to be clean containing only minor trimethylsilyl impurities. Again, **420** was used crude for Pauson-Khand studies and the TMS ether was removed before any purification of Pauson-Khand reactions was carried out. In case of this substrate we hoped to isolate **422**, after retro-aldol reaction of Pauson-Khand adduct **421** (**Scheme 131**).



Scheme 131

The Pauson-Khand reaction of **420** promoted by *n*-butyl methyl sulfide[29] led to the isolation of the compound **419** (**Figure 16**) in 34% yield as in the case of terminal alkyne silyl enol ether **417**. This indicated that some of the substrate **420** did not react and only acid work up after the Pauson-Khand reaction accounted for the loss of the TMS moiety of the cyclobutanone in substrate **420**. Various other unidentifiable products were also isolated from the reaction mixture. The Pauson-Khand reaction of **420** in toluene at reflux also generated complex reaction mixture. Compound **419** was isolated in 3% yield.

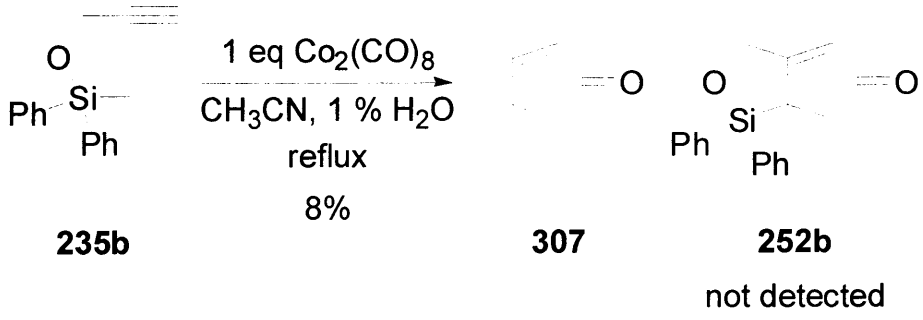
2.4.8 Conclusion

The synthesis of important intermediate cyclobutanone **396** was achieved via a high yielding route. Two trimethylsilyl enol ethers **417** (terminal alkyne) and **420** (TMS substituted alkyne) were synthesized using LHMDS as a base and subjected to Pauson-Khand reaction, however desired compounds were not isolated in either case.

3. Conclusion and Future Work

Silicon tethered enynes as substrates for Pauson-Khand reaction

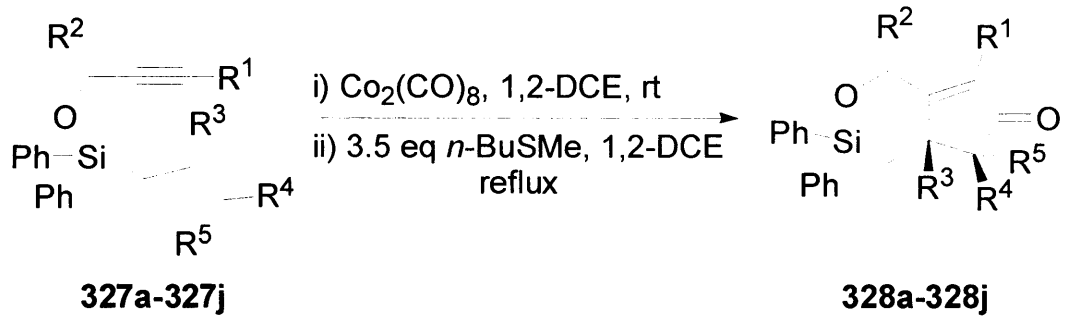
Vinylsilane derived enynes such as **235b** undergo a new type of reductive Pauson-Khand reaction[85,86] and leads to the synthesis of **307** rather than expected **252b**, as reported by Pagenkopf (**Scheme 132**). In these vinylsilane derived enynes, carbons bound to the silicon tether are reduced during the course of the reaction and monocyclic cyclopentenones are formed instead of the expected bicyclic cyclopentenones. Pauson-Khand reaction of substrate **235b** using Pagenkopf's reaction conditions yielded cyclopentenone **307** in 8% yield. Usually in order to synthesise monocyclic cyclopentenones, high pressures of ethylene gas as well as high temperature are required. This new method is superior to the reaction with ethylene for two main reasons; (i) the reaction does not require high pressures or special equipment and (ii) the use of traceless tether circumvents the regiochemical ambiguity observed in the carbonyl insertion when ethylene is used.



Scheme 132

The failure of vinylsilane derived enynes to undergo Pauson-Khand reaction to form bicyclic cyclopentenones led to the synthesis of allylsilane derived enynes as substrates for Pauson-Khand reaction. These silicon tethered substrates do undergo Pauson-Khand reaction and the best yields of bicyclic cyclopentenones were obtained when *n*-butyl methyl sulfide was used as a promoter of the reaction. However, the desired bicyclic cyclopentenones were obtained in only moderate to poor yields. Several different enynes were prepared with varying substituents at various positions and subjected to the

sulfide promoted Pauson-Khand reaction (**Scheme 133**). The results of these studies show that substrate scope for silicon tethered Pauson-Khand reaction is currently limited. Yields of this reaction are low and this is attributed in part to the purification problems associated with these cycloadducts and it is hoped that removal of the silicon tether before any flash column chromatography may lead to easier isolation and enhanced yields of the desired compounds.



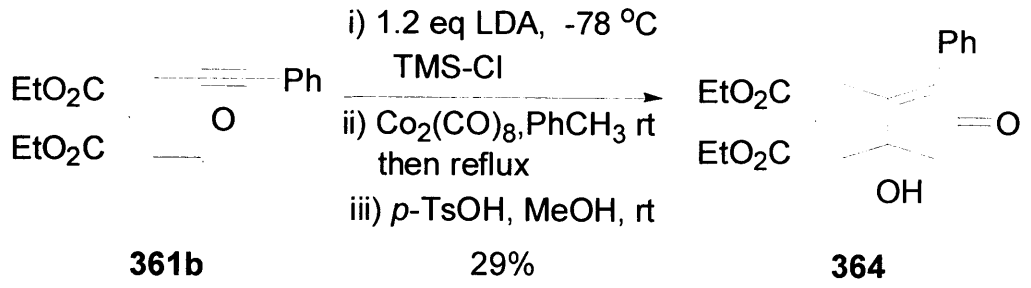
327a-327j **328a-328j**

Scheme 133

Future work on this methodology would thus involve the removal of the silicon tether by various different methods available, (*e.g.* Tamao oxidation, use of TBAF) before any purification of the reaction mixture. Future work on this methodology would also involve investigation and optimisation of catalytic Pauson-Khand reaction conditions to effect the cyclisation of allylsilane derived enynes.

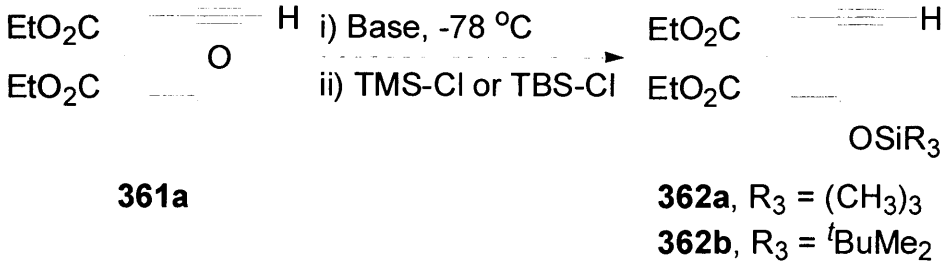
Silyl enol ethers as substrates for the Pauson-Khand reaction

The trimethylsilyl enol ether derived from diethyl malonate derivative **361b** undergoes Pauson-Khand reaction to yield β-hydroxycyclopentenone **364** in 29% yield over 3 steps (**Scheme 134**).



Scheme 134

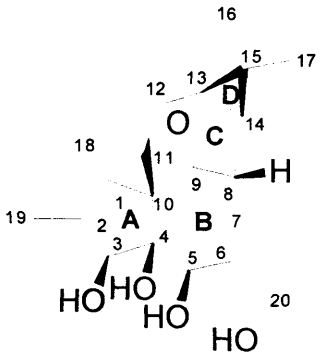
TMS or TBS enol ethers of the terminal alkyne substrate **361a** could not be synthesised (**Scheme 135**).



Scheme 135

The TIPS enol ether of the substrate **361b** yielded the desired bicyclic cyclopentenone in only 13% yield whereas the TIPS enol ethers of the terminal alkyne substrate **361a** did not undergo Pauson-Khand reaction at all. These results indicate that TIPS may be too sterically demanding a group for the Pauson-Khand reaction to take place.

This methodology was applied to the synthesis of a model substrate for ingenol. Ingenol **372** (**Figure 17**), is a highly oxygenated tetracyclic diterpene which possesses a unique structure and an array of biological properties. The most imposing obstacle to the synthesis of ingenol is the establishment of highly strained 'inside-outside' or *trans* intrabridgehead stereochemistry of the B, C ring system.

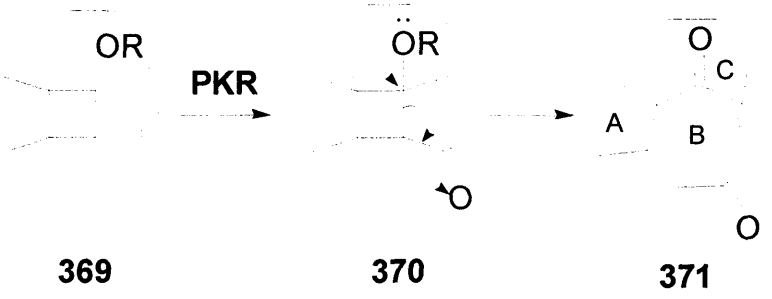


Ingenol

372

Figure 17

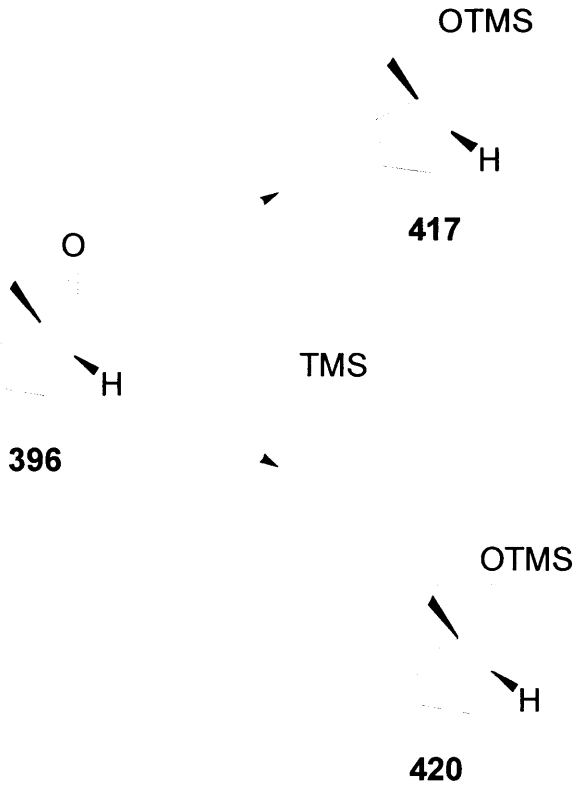
We hoped that the Pauson-Khand reaction of a silyl enol ether of type **369** would lead to intermediate **370**. The retro aldol reaction of this highly strained intermediate **370** would hence lead to the synthesis of A, B and C rings of Ingenol (**Scheme 136**).



369 **370** **371**

Scheme 136

The important intermediate cyclobutanone **396** and its trimethylsilyl enol ethers **417** and **420** were successfully synthesised and subjected to various Pauson-Khand cyclisation conditions, both thermal (toluene, reflux and acetonitrile, reflux) and sulfide promoted (**Scheme 137**). Unfortunately neither yielded the desired compounds containing the ingenane ring skeleton.



Scheme 137

Future work would involve a comprehensive study of Pauson-Khand reaction of the two silyl enol ethers **417** and **420** under a more extensive range of literature conditions for promoting Pauson-Khand reactions.

4. EXPERIMENTAL

4.1 General Experimental Procedures

Melting points were obtained using a Reichert-Jung thermovar hot stage apparatus and are uncorrected.

Proton NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants are recorded in Hertz to the nearest 0.1 Hz.

Carbon-13 NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on Bruker AMX400 spectrometer or 125 MHz on Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Where indicated, carbon-13 NMR were recorded in the presence of a small amount of $Cr(acac)_3$. Where necessary, carbon atoms were assigned using DEPT, HMQC and HMBC experiments. NOE experiments were carried out on a Bruker AVANCE500 spectrometer.

Infrared spectra were recorded as thin films, KBr discs or $CHCl_3$ casts on a SHIMADZU FT-IR 8700 Fourier transform spectrometer. Major features of each spectrum are reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

Low-resolution and high-resolution mass spectra were recorded by the University of London Intercollegiate Research Service and by John Hill (UCL chemistry department service). Low-resolution mass spectra were recorded on a Micromass 70-SE spectrometer and a Micromass ZAB-SE spectrometer using chemical ionisation (CI), electron impact (EI), fast atom bombardment (FAB) or electrospray (esp). Mass spectra marked * were obtained using a Micromass ZAB-SE spectrometer at The University of

London School of Pharmacy. Only molecular ions, fragments from molecular ions and major peaks are reported. High-resolution mass spectra were recorded on a Micromass 70-SE spectrometer.

Microanalyses were performed by Mrs. J. Maxwell, Christopher Ingold Laboratories on a Perkin Elmer 2400 CHN elemental analyser.

Flash chromatography was carried out on BDH silica gel (40-63 μm), Aldrich neutral aluminium oxide (deactivated with 6 wt% water (Grade III), *ca.* 150 mesh) or Acros Florisil® (100-200 mesh). Thin layer chromatography was performed on pre-coated, aluminium-backed normal phase Merck gel 60 F_{254} silica plates. Components were visualised by the quenching of u.v. fluorescence (λ_{max} 254 nm) as well as staining with iodine, vanillin, potassium permanganate or phosphomolybdic acid, all followed by heat.

All reactions in non-aqueous solution were performed under an inert atmosphere of nitrogen or argon, using anhydrous solvents. All glassware was oven-dried (120 °C) and the glassware used for moisture sensitive reactions was flame dried and cooled under a nitrogen or argon atmosphere prior to use.

All solvents were distilled before use. Anhydrous dichloromethane, benzene, toluene, 1,2-dichloroethane and diisopropylamine were obtained by distillation from calcium hydride under a nitrogen atmosphere. Anhydrous diethyl ether and anhydrous THF were obtained by distillation from sodium/benzophenone ketyl under a nitrogen atmosphere. Anhydrous dimethyl sulfoxide, and *N,N*-dimethylformamide were obtained by stirring over calcium hydride followed by distillation under reduced pressure. Anhydrous acetonitrile was obtained by stirring over phosphorus pentoxide followed by distillation. Petroleum ether 30-40 refers to the fraction of light petroleum ether boiling between 30-40 °C, petroleum ether 40-60 refers to the fraction of light petroleum ether boiling between 40-60 °C and petroleum ether 60-80 refers to the fraction of light petroleum ether boiling between 60-80 °C. Ether refers to diethyl ether.

All other reagents were purified in accordance with the methods described in D. D. Perrin and W. L. F. Armarego, "Purification of laboratory chemicals", Pergamon Press, Third edition, 1988 or used as obtained from commercial sources

Chemicals were purchased from Sigma-Aldrich Co. Ltd., Lancaster, Fluka, Acros and Avocado.

4.2 Experimental procedures

4.2.1 Synthesis of vinylsilane-derived enynes

Synthesis of 3-(Dimethylvinylsilyloxy)prop-1-yne 235a

Using the procedure of Sieburth *et al.*[80], propargyl alcohol (**256**, 0.20 g, 3.6 mmol), chlorodimethylvinylsilane (**244a**, 0.51 mL, 3.8 mmol) and diisopropylethylamine (0.68 mL, 3.9 mmol) were stirred in benzene (3 mL) at rt under nitrogen overnight.

Diethyl ether (5 mL) was added and the reaction mixture was washed with H_2O (2 x 10 mL). The ethereal extract was dried (Na_2SO_4) and concentrated *in vacuo* to obtain an oil which was purified by flash chromatography (SiO_2, Petrol 60-80 / Ether 99 : 1) to obtain 3-(dimethylvinylsilyloxy)prop-1-yne (**235a**, 39 mg, 8%) as a pale yellow oil.

δ_H (300 MHz; $CDCl_3$) 6.15 (1H, dd, *J* 20.1, 14.9, CH_2=C*H*), 5.95 (1H, dd, *J* 14.8, 4.1, 1 of CH_2=CH (*cis*)), 5.76 (1H, dd, *J* 20.1, 4.1, 1 of CH_2=CH (*trans*)), 4.22 (2H, d, *J* 2.4, HC≡CCH_2), 2.40 (1H, t, *J* 2.4, *H*C≡CCH_2), 0.10 (6H, s, 2 x CH_3).

Synthesis of 3-(Diphenylvinylsilyloxy)prop-1-yne 235b

Using the procedure of Sieburth *et al.*[80], propargyl alcohol (**235b**, 0.40 g, 7.1 mmol), chlorodiphenylvinylsilane (**244b**, 1.66 mL, 7.5 mmol) and triethylamine (1.1 mL, 7.9 mmol) were stirred at rt in dry dichloromethane (6 mL) overnight under nitrogen.

Diethyl ether (10 mL) was added to the reaction mixture, which was washed with H_2O (2 x 20 mL). The combined aqueous layers were extracted with diethyl ether (2 x 10

mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to obtain 3-(diphenylvinylsilyloxy)prop-1-yne (**235b**, 1.88 g, 100%) as a clear yellow oil .

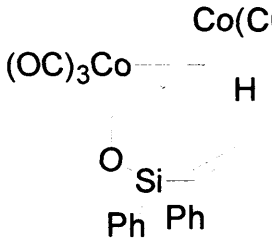
120 mg of the product was subjected to flash chromatography (Al_2O_3, Petrol 30-40 / Ether 99 : 1) which led to the decomposition product diphenylvinylsilanol (**273**, 61.3 mg, 52%)

ν_{max} (neat)/cm^{-1} 3267s (O-H), 3049m (=C-H_2), 3000w (C-H), 1591m (C=C), 1428s, 1405m; δ_H (300 MHz; $CDCl_3$) 7.66-7.62 (4H, m, arom.*H*), 7.42-7.36 (6H, m, arom.*H*), 6.51 (1H, dd, *J* 20.2, 14.9, *H*C=CH_2), 6.27 (1H, dd, *J* 14.9, 3.8, 1 of HC=CH_2 (*cis*)), 5.95 (1H, dd, *J* 20.2, 3.8, 1 of HC=CH_2 (*trans*)), 2.30 (1H, s, O*H*); δ_C (75 MHz, $CDCl_3$) 136.5 (HC=*C*H_2), 135.2 (arom.C_q), 134.61 (H*C*=CH_2), 134.60 (arom.*C*H), 130.1 (arom.*C*H), 127.9 (arom.*C*H); *m/z* (FAB pos)* 227 (MH^+, 12%), 209 (68), 199 (63), 149 (100), 123 (76), 105 (51).

140 mg of the crude silyl ether was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 99 : 1) to obtain 3-(diphenylvinylsilyloxy)prop-1-yne (**235b**, 0.10 g, 73%) as an oil.

Found C 77.2, H 6.2; $C_{17}H_{16}OSi$ requires C 77.2, H 6.1%; ν_{max} (neat)/cm^{-1} 3296m (C≡C-H), 3069m (=C-H_2), 3051m (C-H), 1591m (C=C), 1429s, 1404m, 1371m; δ_H (300 MHz; $CDCl_3$) 7.66-7.63 (4H, m, arom.*H*), 7.45-7.37 (6H, m, arom.*H*), 6.53 (1H, dd, *J* 20.2, 14.9, *H*C=CH_2), 6.31 (1H, dd, *J* 15.0, 3.9, 1 of HC=CH_2 (*cis*)), 5.96 (1H, dd, *J* 20.1, 3.8 Hz, 1 of HC=CH_2 (*trans*)), 4.42 (2H, d, *J* 2.4, H_2CC≡C-H), 2.39 (1H, t, *J* 2.4, H_2CC≡C-*H*); δ_C (75 MHz, $CDCl_3$) 137.6 (HC=*C*H_2), 135.1 (arom.*C*H), 133.4 (arom.C_q), 132.9 (H*C*=CH_2), 130.2 (arom.*C*H), 127.9 (arom.*C*H), 81.7 (HC≡*C*), 73.5 (H*C*≡C), 52.0 (O*C*H_2); *m/z* (FAB pos) 265 (MH^+, 20%), 209 (MH^+-CH≡CCH_2OH, 100), 183 (54), 157 (96), 133 (65), 105 (42).

Synthesis of Dicobalt hexacarbonyl complex of 3-(diphenylvinylsilyloxy)prop-1-yne 279

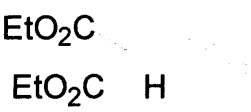


Using the procedure of Mukai *et al.*[91], a solution of 3-(diphenylvinylsilyloxy)prop-1-yne (**235b**, 0.10 g, 0.4 mmol) in hexane (3 mL) was added to dicobalt octacarbonyl (0.16 g, 0.45 mmol), weighed under nitrogen in a glove bag and stirred at rt for 40 minutes.

The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2, hexane / Ether 99 : 1 to 50 : 50) to obtain the dicobalt hexacarbonyl complex of 3-(diphenylvinylsilyloxy)prop-1-yne (**279**, 0.10 g, 46%) as a dark red oil.

δ_H (300 MHz; $CDCl_3$) 7.64 (4H, br s, arom.*H*), 7.41 (6H, br s, arom.*H*), 6.48 (1H, br d, *J* 18.2, *H*C=CH_2), 6.31 (1H, br d, *J* 11.5, HC=CH_2 *cis*), 5.99-5.90 (1H, m, HC=CH_2 *trans*), 5.89 (1H, br s, OCH_2CCH), 4.93 (2H, br s, OCH_2).

Synthesis of Diethyl propargylmalonate 276a



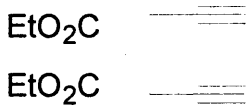
Using the procedure of Marvel and Hager[89], diethyl malonate (**274**, 15.5 g, 97 mmol) was added to a solution of sodium ethoxide prepared by the addition of sodium (1.93 g, 84 mmol), in small pieces, to ethanol (37 mL) under nitrogen. The reaction mixture was warmed to 50 °C and propargyl bromide (**275**, 12.5 mL, 84 mmol) was added dropwise. The reaction mixture was heated to reflux for 4 h.

Ethanol was removed *in vacuo* and H_2O (30 mL) was added. The organic layer was removed and the aqueous layer was extracted with diethyl ether (5 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Toluene / EtOAc 99 : 1) afforded diethyl propargylmalonate (**276a**, 7.5 g, 45%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3287s (C≡C-H), 2984s & 2939m (C-H), 2160w (C≡C), 1734s (C=O), 1467m, 1447m, 1428m, 1370s; δ_H (300 MHz; $CDCl_3$) 4.23 (2H, dq, *J* 10.8, 7.2, 2 of OCH_2), 4.20 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.55 (1H, t, *J* 7.7, O_2CCHCO_2), 2.77 (2H, dd *J* 7.7, 2.7, H_2CC≡CH), 2.00 (1H, t, *J* 2.7, C≡C*H*), 1.27 (6H, t, *J* 7.2, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 167.8 (*C*=O), 80.0 (*C*≡CH), 70.3 (C≡*C*H), 61.7 (OCH_2), 51.2

(O_2CCHCO_2), 18.4 ($H_2CC{\equiv}CH$), 14.0 (OCH_2CH_3); *m/z* (FAB pos) 221 (MNa^+, 28%), 217 (50), 176 (100); HRMS calculated for $C_{10}H_{14}O_4$ (MNa^+) 221.0790 Found 221.0793.

A side product of the reaction diethyl dipropargylmalonate (**277a**, 2.4 g, 12%) was isolated as a white crystalline solid.



m.p.: 46 °C; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3291s (C≡C-H), 2984s (C-H), 2150w (C≡C), 1738s (C=O), 1466m, 1447m, 1429m, 1368m; δ_H (300 MHz; $CDCl_3$) 4.22 (4H, q, *J* 7.2, OCH_2), 2.98 (4H, d *J* 2.7, $H_2CC{\equiv}CH$), 2.02 (2H, t, *J* 2.7, C≡C*H*), 1.25 (6H, t, *J* 7.2, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 168.6 (*C*=O), 78.4 (*C*≡CH), 71.6 (C≡*C*H), 62.0 (OCH_2), 56.2 (O_2CCCO_2), 22.5 ($H_2CC{\equiv}CH$), 14.0 (OCH_2CH_3); *m/z* (CI pos) 237 (MH^+, 62%), 191 (100), 153 (46), 111 (77); HRMS calculated for $C_{13}H_{16}O_4$ (MH^+) 237.1127 Found 237.1117.

Synthesis of Diethyl allylpropargylmalonate 59

Using the procedure of Trost *et al.*[90], a mixture of diethyl propargyl malonate (**274**, 0.85 g, 4.3 mmol), allyl bromide (**278**, 1.56 g, 12.9 mmol) and K_2CO_3 (1.78 g, 12.9 mol) in acetone (15 mL) under nitrogen was heated to reflux overnight.

The reaction mixture was filtered and concentrated to obtain a yellow oil, which was purified by flash chromatography (SiO_2, hexane / Ether 4 : 1) to obtain diethyl allylpropargylmalonate (**59**, 0.55 g, 54%) as a clear colourless oil.

Found C 65.4 H 7.8; $C_{13}H_{18}O_4$ requires C 65.5 H 7.6% ; ν_{max} (neat)/cm^{-1} 3287m (C≡C-H), 2982m & 2937w (C-H), 1738s (C=O), 1650w (C=C), 1443m, 1367m; δ_H (500 MHz; $CDCl_3$) 5.62 (1H, ddt, *J* 17.5, 10.1, 7.5, *H*C=CH_2), 5.18 (1H, ddt, *J* 17.0, 1.9, 1.3, 1 of HC=CH_2 (*trans*)), 5.12 (1H, ddt, *J* 10.1, 2.0, 1.0, 1 of HC=CH_2 (*cis*)), 4.21 (4H, q, *J* 7.2, OCH_2), 2.80 (2H, dt, *J* 7.5, 1.0, H_2CHC=CH_2), 2.79 (2H, d, *J* 2.7, HC≡CCH_2), 2.01 (1H, t, *J* 2.7, *H*C≡C), 1.25 (6H, t, *J* 7.2, CH_3); δ_C (125 MHz, $CDCl_3$) 169.7 (*C*=O), 131.7 (H_2C=*C*H), 119.8 (H_2C=CH), 78.9 (HC≡*C*), 71.4 (*H*C≡C), 61.7 (OCH_2), 56.6 (CO_2CCO_2), 36.3 (H_2C=CHCH_2), 22.5 (HC≡CCH_2), 14.0 (CH_3); *m/z* (FAB pos)* 239 (MH^+, 100%), 137 (49), 105 (10).

Synthesis of Diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate 61

Method 1

A solution of dicobalt octacarbonyl (0.17 g, 0.5 mmol) in dichloromethane (3 mL) was added to diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) and stirred at rt under nitrogen for 1 h. The reaction mixture was concentrated to obtain a reddish brown residue which was purified by flash chromatography (Petrol 30-40 / Et_2O 99 : 1) to obtain a brown oil. The ^1H NMR spectrum was broad and inconclusive, however IR showed a Co-C≡O stretch at 2100 cm^{-1}. The complex (**60**) was heated to reflux in toluene (2 mL) for 1 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo* to obtain a brown solid which was purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to obtain diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 18 mg, 30%) as a light yellow oil.

Method 2

Using the procedure of Mukai *et al.*[91], a solution of dicobalt octacarbonyl (0.17 g, 0.5 mmol) in dichloromethane (4 mL) was added to diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) and stirred at rt under nitrogen for 1 h. The reaction mixture was concentrated to obtain the crude complex (**60**), which was dissolved in acetonitrile (5 mL) and heated at 75 °C under nitrogen for 1 h. The mixture was concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 49.8 mg, 44%) as a yellow oil.

Method 3

Using the procedure of Schreiber *et al.*[25], a solution of dicobalt octacarbonyl (0.17 g, 0.5 mmol) in dichloromethane (3 mL) was added to diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) and stirred at rt under nitrogen for 1 h. The reaction mixture was concentrated *in vacuo* to obtain the complex (**60**), which was dissolved in THF (15 mL) and added to *N*-methylmorpholine-*N*- oxide monohydrate (0.40 g, 3 mmol), at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 4 h, then filtered through Celite®,

concentrated *in vacuo* and purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 29.0 mg, 23%) as a yellow oil.

Method 4

Using the procedure of Sugihara *et al.*[28], a solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in ether (3 mL) was added to dicobalt octacarbonyl (0.17 g, 0.50 mmol), weighed under nitrogen in a glove bag. The resulting mixture was stirred at rt under nitrogen for 30 minutes, then concentrated *in vacuo* and the resulting complex dissolved in 1:3 dioxane/2 M NH_4OH (4.20 mL) and heated at 100 °C for 1 h. Diethyl ether (10 mL) was added to the reaction mixture and the resulting suspension filtered through cotton wool. The filtrate was washed with H_2O (2 x 50 mL) and the combined aqueous layers were extracted with diethyl ether (4 x 20 mL). The ethereal extracts were combined and successively washed with 5% HCl (2 x 50mL), saturated $NaHCO_3$ (2 x 50mL), dried ($MgSO_4$), and concentrated *in vacuo* to obtain the crude product which was purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 35 mg, 31%) as a yellow oil.

Method 5

Using the procedure of Sugihara *et al.*[29], a solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in 1,2-dichloroethane (4.2 mL) was added to dicobalt octacarbonyl (0.17 g, 0.5 mmol), which was weighed in a glove bag under nitrogen and stirred at rt for 20 minutes. *n*-Butyl methyl sulfide (0.15 g, 1.5 mmol) was added to the reaction mixture and heated to reflux for 50 minutes.

The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to obtain diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 38 mg, 34%) as a yellow oil.

Method 6

Using the procedure of Smit *et al.*[31], a solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in ether (3 mL) was added to dicobalt octacarbonyl (0.17 g, 0.5 mmol), which was weighed under nitrogen in a glove bag, and stirred at rt for 15 minutes. The reaction mixture was concentrated *in vacuo* and the resulting dark

orange/brown complex was dissolved in pentane (15 mL). Silica gel (3.8 g) was added and the reaction mixture was agitated on a rotary evaporator at atmospheric pressure for 40 minutes. The solvent was removed *in vacuo* and the residue was heated to 50 °C on a rotary evaporator for 3.5 h in a stream of air. The residue was loaded directly onto a flash chromatography column. Flash chromatography (SiO_2, hexane / EtOAc 7 : 3) afforded diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 62 mg, 55%) as a slightly yellow oil.

Method 7

Dicobalt octacarbonyl (0.17 g, 0.50 mmol) was weighed into a pressure tube under nitrogen in a glove bag. A solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in acetonitrile (5 mL) was added and the mixture was stirred at rt for 1 h. Carbon monoxide was bubbled through the solution for 1 minute and the sealed tube was then heated at 75 °C for 2.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 28 mg, 25%) as a yellow oil.

Method 8

Dicobalt octacarbonyl (0.20 g, 0.6 mmol) was weighed into a pressure tube under nitrogen in a glove bag. A solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in toluene (5 mL) was added and the reaction mixture was stirred at rt for 30 minutes. Carbon monoxide was bubbled through the solution for about 1 minute and the sealed tube was then heated at 80 °C overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 17 mg, 15%) as a yellow oil.

Method 9

Dicobalt octacarbonyl (0.19 g, 0.55 mmol) was weighed into a pressure tube under nitrogen in a glove bag. A solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in toluene (5 mL) was added and the reaction mixture was stirred at rt for 20 minutes. Carbon monoxide was bubbled through the solution for 1 minute and the

sealed tube was heated at 110 °C for 6 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to afford diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 23 mg, 20%) as a pale yellow oil.

Method 10

A solution of diethyl allylpropargylmalonate (**59**, 0.10 g, 0.4 mmol) in degassed hexane (3 mL) was added to dicobalt octacarbonyl (0.17 g, 0.5 mmol), weighed into a pressure tube in a glove bag under nitrogen, and stirred at rt for 20 minutes. Carbon monoxide was bubbled through the reaction mixture for 1 minute and the sealed pressure tube was heated to 69 °C for 1.5 h.

The reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, hexane / EtOAc 7 : 3) to obtain diethyl 3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (**61**, 65 mg, 58%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 2983m & 2937s (C-H), 1732s (C=O ester), 1713s (C=O ketone), 1635s (C=C), 1447s, 1367s; δ_H (400 MHz; $CDCl_3$) 5.93 (1H, br s, *H*C=C), 4.24 (2H, q, *J* 7.1,OC*H*$_2$), 4.20 (2H, q, *J* 7.1, OC*H*$_2$), 3.35 (1H, d, *J* 19.0, 1 of *H*$_2$CC=CH), 3.25 (1H, d, *J* 18.8, 1 of *H*$_2$CC=CH), 3.10-3.05 (1H, m, H_2CCHCH_2), 2.79 (1H, dd, *J* 12.8, 7.7, 1 of OCC*H*$_2$), 2.63 (1H, dd, *J* 17.9, 6.4, 1 of C*H*$_2$CHCH_2), 2.13 (1H, dd, *J* 17.9, 3.3, 1 of C*H*$_2$CHCH_2), 1.73 (1H, t, *J* 12.7, 1 of OCC*H*$_2$), 1.28 (3H, t, *J* 7.1, C*H*$_3$), 1.25 (3H, t, *J* 7.1, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 209.5 (*C*=O ketone), 185.5 (*C*=O ester), 171.5 (*C*=O ester), 170.4 (*C*=CH), 125.6 (C=*C*H), 62.1 (O*C*H$_2$), 62.0 (O*C*H$_2$), 60.8 (CO_2CCO_2), 45.0 (*C*H), 42.1 (HC=C*C*H$_2$), 38.9 (OC*C*H$_2$), 35.1 (*C*H$_2$CHCH$_2$), 14.0 (*C*H$_3$); *m/z* (EI)* 267 (MH^+, 40%), 266 (M^+, 99), 221 (50), 192 (100), 173 (55), 165 (68); HRMS calculated for $C_{14}H_{19}O_5$ (MH^+) 267.1240 Found 267.1232.

Synthesis of Dimethyl(3-phenylprop-2-ynyloxy)vinylsilane 286[86]

Chlorodimethylvinylsilane (**244a**, 0.22 mL, 1.6 mmol) was added dropwise to a solution of 3-phenyl-2-propyn-1-ol (**329**, 0.20 g, 1.5 mmol) and triethylamine (0.23 mL, 1.7 mmol) in dichloromethane (10 mL) under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes and then at rt overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (10 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, hexane / EtOAc 97 : 3) afforded dimethyl(3-phenylprop-2-ynyloxy)vinylsilane (**286**, 0.20 g, 60%) as a clear yellow oil.

ν_{max} (neat)/cm^{-1} 3013m (=C-H_2), 2959m & 2856m (C-H), 2280w (C≡C), 1595w (C=C), 1489s (C=C aromatic), 1367s, 1256s; δ_H (300 MHz; $CDCl_3$) 7.45-7.41 (2H, m, arom.*H*), 7.31-7.28 (3H, m, arom.*H*), 6.21 (1H, dd, *J* 20.0, 15.0, H_2C=C*H*), 6.07 (1H, dd, *J* 15.0, 4.4, 1 of H_2C=CH (*cis*)), 5.85 (1H, dd, *J* 20.0, 4.4, 1 of H_2C=CH (*trans*)), 4.52 (2H, s, OCH_2), 0.29 (6H, s, 2 x CH_3); δ_C (75 MHz; $CDCl_3$) 136.9 (HC=CH_2), 133.7 (SiCH), 131.6 (arom.CH), 128.3 (arom.CH), 128.2 (arom.CH), 122.9 (arom.C_q), 87.5 (PhC≡C), 85.1 (OCH_2C≡C), 51.8 (OCH_2), -1.9 (2 x CH_3); *m/z* (EI) 216 (M^+, 18%), 201 (65), 171 (100), 115 (89), 75 (60).

Synthesis of 3-Methyl-2-phenylcyclopent-2-enone 215[86]

A solution of dimethyl(3-phenylprop-2-ynyloxy)vinylsilane (**286**, 0.14 g, 0.63 mmol) in acetonitrile (0.5 mL) was added to a stirred solution of dicobalt octacarbonyl (0.22 g, 0.63 mmol) and H_2O (23 μL, 1.3 mmol) in acetonitrile (2.5 mL), under nitrogen. After stirring for 1h at rt, the reaction flask was placed into a preheated oil bath (135 °C) to bring the reaction mixture quickly to reflux. After 30 minutes the reaction flask was removed from the oil bath and allowed to cool to rt. The volatile components were removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, hexane / EtOAc 3 : 2) to afford 3-methyl-2-phenylcyclopent-2-enone (**215**, 69 mg, 63%) as a pale yellow oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2922s & 2852s (C-H), 1682s (C=O), 1634s (C=C), 1595m (C=C aromatic), 1495m (C=C aromatic), 1464s, 1379s; δ_H (300 MHz; $CDCl_3$) 7.41-7.36 (2H, m, arom.*H*), 7.31-7.27 (3H, m, arom.*H*), 2.66-2.63 (2H, m, OCCH_2), 2.55-2.52 (2H, m, $OCCH_2CH_2$), 2.16 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 207.4 (*C*=O), 171.5 & 140.4 (*C*=*C*), 131.8 (arom.C_q), 129.1 (arom.CH), 128.2 (arom.CH), 127.5 (arom.CH), 34.8 ($OCCH_2$), 31.8 ($OCCH_2CH_2$), 18.3 (CH_3); *m/z* (EI) 172 (M^+, 11%) , 129 (86) , 115 (100).

Synthesis of 3-Methylcyclopent-2-enone

Using the procedure of Pagenkopf *et al.*[86], a solution of 3-(diphenylvinylsilyloxy)prop-1-yne (**235b**, 0.19 g, 0.72 mmol) in acetonitrile (0.66 mL) was added to a stirred solution of dicobalt octacarbonyl (0.22 g, 0.7 mmol) and H_2O (26 μL, 1.4 mmol) in acetonitrile (2.9 mL) under nitrogen. After stirring for 1h at rt, the reaction flask was placed into a preheated oil bath (135 °C) to bring the reaction mixture quickly to reflux. After 30 minutes the reaction flask was removed from the oil bath and allowed to cool to rt. The volatile components were removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, hexane / EtOAc 3 : 2) to afford 3-methylcyclopent-2-enone (**307**, 5 mg, 8%) as a pale yellow oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2924m & 2361s (C-H), 1618 br, m (C=O + C=C); δ_H (300 MHz; $CDCl_3$) 5.95 (1H, s, C=C*H*), 2.59-2.57 (2H, m, OCCH_2), 2.43-2.40 (2H, m, OCCH$_2$CH_2), 2.14 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 209.5 (*C*=O), 178.7 (H_3C*C*=CH), 130.3 (H_3CC=*C*H), 35.4 (OC*C*H$_2$), 32.7 (OCCH$_2$*C*H$_2$), 19.1 (*C*H$_3$); *m/z* (EI) 96 (M^+, 100%); HRMS calculated for C_6H_8O (M^+) 96.0575, Found 96.0571.

4.2.2 Synthesis of allylsilane-derived enynes

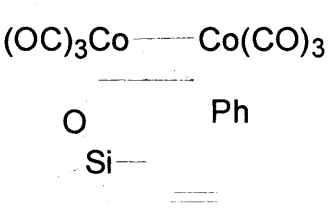
Synthesis of Allyldimethyl(3-phenylprop-2-ynyloxy)silane 327a

Using the procedure of Pagenkopf *et al.*[86], allylchlorodimethylvinylsilane (**330a**, 0.34 mL, 2.2 mmol) was added dropwise to a solution of 3-phenyl-2-propyn-1-ol (**329**, 0.31 g, 2.4 mmol) and triethylamine (0.62 mL, 4.5 mmol) in dichloromethane (8 mL) under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes and then at rt overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (8 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed successively with H_2O (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and then concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Petrol 40-60 / Ether 98 : 2) afforded allyldimethyl(3-phenylprop-2-ynyloxy)silane (**327a**, 0.14 g, 78%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 3077m (=C-H$_2$), 2959m & 2859m (C-H), 1630s (C=C), 1599m (C=C aromatic), 1490s (C=C aromatic), 1443m, 1419m, 1368s; δ_H (400 MHz; $CDCl_3$) 7.46-7.43 (2H, m, arom.*H*), 7.33-7.30 (3H, m, arom.*H*), 5.85 (1H, ddt, *J* 16.8, 10.0, 8.1, SiCH$_2$C*H*), 4.97-4.89 (2H, m, C=C*H*$_2$), 4.55 (2H, s, OC*H*$_2$), 1.74 (2H, d, *J* 8.1, SiC*H*$_2$), 0.23 (6H, s, 2 x C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 133.7 (H*C*=CH$_2$), 131.6 (arom.*C*H), 128.32 (arom.*C*H), 128.26 (arom.*C*H), 122.8 (arom.*C*$_q$), 114.0 (=*C*H$_2$), 87.4 & 85.1 (*C*≡*C*), 51.9 (O*C*H$_2$), 24.5 (Si*C*H$_2$), -2.3 (2 x *C*H$_3$); *m/z* (CI pos) 230 (M$^+$, 41%), 229 (62), 189 (100), 115 (79).

Synthesis of Dicobalt hexacarbonyl complex of Allyldimethyl(3-phenylprop-2-ynyloxy)silane 331a



Using the procedure of Mukai *et al.*[91], a solution of allyldimethyl(3-phenylprop-2-ynyloxy)silane (**327a**, 0.10 g, 0.4 mmol) in dichloromethane (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.39 g, 1.1 mmol) in dichloromethane (2 mL), under nitrogen at rt,. The resulting reaction mixture was stirred at rt for 1 h and then concentrated *in vacuo* at rt. The residue was purified by flash chromatography (Florisil®, Petrol 40-60) to afford dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (**331a**, 0.20 g, 89%) as a deep red oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2960w (=C-H), 2918m (C-H), 2091s & 2051s (Co-C≡O), 1650m (C=C), 1475m (C=C aromatic), 1425m, 1258s; δ_H (300 MHz; $CDCl_3$) 7.54-7.52 (2H, br m, arom.*H*), 7.34-7.32 (3H, br m, arom.*H*), 5.92-5.78 (1H, br m, *H*C=CH$_2$), 5.01 (2H, br s, OC*H*$_2$), 4.97-4.88 (2H, br m, C=C*H*$_2$), 1.72 (2H, br d, *J* 7.9, SiC*H*$_2$), 0.21 (6H, s, 2 x C*H*$_3$); δ_C (75 MHz; $CDCl_3$ + Cr(acac)$_3$) 199.5 (*C*=O), 137.8 (arom.*C*$_q$), 133.7 (H*C*=CH$_2$), 129.7 (arom.*C*H), 128.8 (arom.*C*H), 127.8 (arom.*C*H), 114.0 (HC=*C*H$_2$), 97.1 & 89.7 ((OC)$_3$Co*C*-*C*Co(CO)$_3$), 63.5 (O*C*H$_2$), 24.3 (Si*C*H$_2$), -2.8 (2 x *C*H$_3$); *m/z* (ES pos) 413 (37), 349 (29), 305 (45), 301 (39), 261 (100).

Synthesis of 3,3-Dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328a

Method 1

A solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (**331a**, 0.10 g, 0.2 mmol) in toluene (1 mL) was heated to reflux under nitrogen for 2 h. The reaction mixture was cooled and concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328a**, 20 mg, 40%) as a yellow oil.

Method 2

Using the procedure of Mukai *et al.*[91], a solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (**331a**, 0.10 g, 0.2 mmol) in acetonitrile (1 mL) was heated to reflux under nitrogen overnight. The reaction mixture was cooled and concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328a**, 20 mg, 39%) as a yellow oil.

Method 3

Using the procedure of Pagenkopf *et al.*[86], a solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (**331a**, 0.10 g, 0.2 mmol) and H_2O (7.7 μL, 0.39 mmol) in acetonitrile (0.77 mL) under nitrogen was heated to reflux overnight. The reaction mixture was cooled and concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328a**, 16 mg, 33%) as a yellow oil.

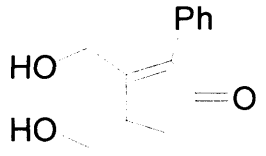
Method 4

Using the procedure of Sugihara *et al.*[29], a solution of dicobalt hexacarbonyl complex of allyldimethyl(3-phenylprop-2-ynyloxy)silane (**331a**, 0.20 g, 0.4 mmol) and *n*-butyl

methyl sulfide (0.17 mL, 1.4 mmol) in 1,2-dichloroethane (3.9 mL) under nitrogen was heated to reflux overnight. The reaction mixture was cooled and concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 100 : 0 to 50 : 50) to afford 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328a**, 72 mg, 72%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 2955m & 2922m (C-H), 1699s (C=O), 1630w (C=C), 1599w (C=C aromatic), 1495m (C=C aromatic), 1445m, 1406m, 1254s; δ_H (400 MHz; $CDCl_3$) 7.42-7.25, (5H, m, arom.*H*), 4.95 (1H, d, *J* 16.3, 1 of OC*H*$_2$), 4.80 (1H, d, *J* 16.3, 1 of OC*H*$_2$), 3.25-3.19 (1H, m, SiCH$_2$C*H*), 2.93 (1H, dd, *J* 18.9, 6.4, 1 of OCC*H*$_2$), 2.25 (1H, dd, *J* 18.2, 1.6, 1 of OCC*H*$_2$) , 1.35 (1H, dd, *J* 14.3, 5.1, 1 of SiC*H*$_2$), 0.76 (1H, t, *J* 13.9, 1 of SiC*H*$_2$), 0.31 (3H, s, C*H*$_3$), 0.21 (3H, s, C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 206.0 (C=O), 173.0 (OCH$_2$*C*=C), 138.0 (C=*C*Ph), 130.7 (arom.*C*$_q$), 128.9 (arom.*C*H), 128.3 (arom.*C*H), 128.1 (arom.*C*H), 62.3 (*O*CH$_2$), 45.8 (OC*C*H$_2$), 35.4 (SiCH$_2$*C*H), 21.6 (Si*C*H$_2$), -0.85 (*C*H$_3$), -2.0 (*C*H$_3$); *m/z* (CI pos) 259 (MH$^+$, 98%), 185 (25), 40 (100); HRMS calculated for $C_{15}H_{19}O_2Si$ (MH$^+$) 259.11543 Found 259.11504.

Synthesis of 3,4-Di(hydroxymethyl)-2-phenylcyclopent-2-enone 332

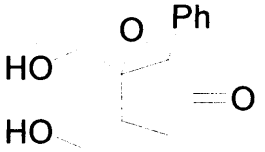


Using the procedure of Tamao *et al.*[92], a solution 3,3-dimethyl-7-phenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328a**, 72 mg, 0.28 mmol) in 1:1 THF/MeOH (0.76 mL) was added to a flask containing potassium hydrogen carbonate (28.0 mg, 0.28 mmol) and potassium fluoride (32.0 mg, 0.56 mmol) under nitrogen at rt. The flask was opened to air and 30% hydrogen peroxide in water (0.11 mL, 0.92 mol) was added in one portion. The resulting reaction mixture was heated at 50 °C for 45 minutes and then stirred at rt overnight. The reaction mixture was concentrated and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / EtOAc 35 : 65) to afford 3,4-di(hydroxymethyl)-2-phenylcyclopent-2-enone (**332**, 9 mg, 15%) as a thick yellow oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3390br s (O-H), 2925s & 2855s (C-H), 1696 br s (C=O), 1605w (C=C aromatic), 1495w (C=C aromatic), 1425m; δ_H (400 MHz; $CDCl_3$) 7.43-7.35 (3H, m, arom.*H*), 7.30-7.27 (2H, m, arom.*H*), 4.68 (1H, d, *J* 14.2, 1 of C=CC*H*$_2$OH), 4.53 (1H, d *J* 14.2, 1 of C=CC*H*$_2$OH), 4.07 (1H, dd, *J* 10.2, 4.4, 1 of HOC*H*$_2$CH), 3.69 (1H,

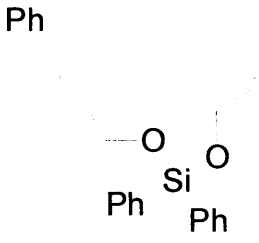
dd, *J* 10.2, 8.8, 1of $HOCH_2CH$), 3.39-3.35 (1H, m, $HOCH_2CH$), 2.75 (1H, dd, *J* 18.8, 7.1, 1 of $OCCH_2$), 2.21 (1H, dd, *J* 18.8, 2.5, 1 of $OCCH_2$); δ_C (100 MHz; $CDCl_3$) 206.0 (*C*=O), 172.2 ($HOCH_2C$=C), 141.5 (C=*C*Ph), 130.6 (arom.C_q), 129.2 (arom.*C*H), 128.38 (arom.*C*H), 128.37 (arom.*C*H), 65.3 ($HOCH_2C$=C), 60.0 ($HOCH_2CH$), 41.8 ($OCCH_2$) 38.1 ($HOCH_2CH$); *m/z* (ES pos) 241 (MNa^+, 100%), 200 (18), 102 (29); HRMS calculated for $C_{13}H_{14}O_3Na$ (MNa^+) 241.0835 Found 241.0842.

18 mg of another impure compound was also isolated and could be tentatively identified as 2,3-epoxy-3,4-di(hydroxymethyl)-2-phenylcyclopentanone **333**, by the following signals in its ^1H NMR spectrum.



δ_H (300 MHz; $CDCl_3$) 3.70 (1H, d, *J* 12.7, 1 of $OCCH_2OH$), 3.50 (1H, d, *J* 12.7, 1 of $OCCH_2OH$), 2.98-2.93 (1H, m, $HOCH_2CH$), 2.79 (1H, dd, *J* 17.9, 8.8, 1 of $HOCH_2CH$), 2.43 (1H, dd, *J* 18.1, 8.7, 1 of $OCCH_2$), 2.15 (1H, dd, *J* 17.9, 1.1, 1 of $HOCH_2CH$), 2.14 (1H, dd, *J* 18.1, 8.4, 1 of $OCCH_2$).

Synthesis of Diphenyldi(3-phenylprop-2-ynyloxy)silane 337

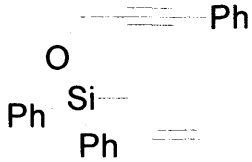


Using the procedure of Wei *et al.*[95], a solution of triethylamine (0.33 mL, 2.4 mmol) and 3-phenyl-2-propyn-1-ol (**329**, 0.21 g, 1.60 mmol) in THF (1.3 mL) was added dropwise to a stirred solution of dichlorodiphenylsilane (**335**, 0.17 mL, 0.79 mmol) in THF (0.4 mL) at rt under argon was added. The reaction mixture was heated to reflux for 2.5 h.

The reaction mixture was quenched with sat. aqueous NH_4Cl (5 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (5 x 15 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 97 : 3) afforded diphenyldi(3-phenylprop-2-ynyloxy)silane (**337**, 0.20 g, 57%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3071s, 3003m & 2922m (C-H), 2359w (C≡C), 1591s (C=C aromatic), 1570m (C=C aromatic), 1489s (C=C aromatic), 1443s, 1429s, 1375s; δ_H (300 MHz; $CDCl_3$) 7.82-7.79 (4H, m, arom.*H*), 7.47-7.36 (10H, m, arom.*H*), 7.31-7.27 (6H, m, arom.*H*), 4.78 (4H, s, OCH_2); δ_C (75 MHz; $CDCl_3$) 135.1 (arom.*C*H), 131.73 (arom.C_q), 131.70 (arom.*C*H), 130.6 (arom.*C*H), 128.3 (arom.*C*H), 128.2 (arom.*C*H), 127.9 (arom.*C*H), 122.8 (arom.C_q), 87.0 & 85.4 (*C*≡*C*), 52.4 (O*C*H$_2$); *m/z* (FAB pos) 467 (MNa^+, 17%), 444 (M^+, 20), 307 (52), 283 (100), 223 (35), 199 (45); HRMS calculated for $C_{30}H_{24}O_2Si$ (M^+) 444.1546 Found 444.1540.

Synthesis of Allyldiphenyl(3-phenylprop-2-ynyloxy)silane 327b



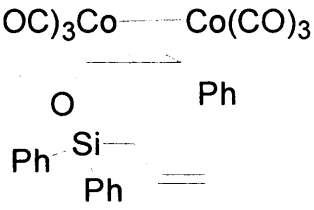
Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 2.3 mL, 2.3 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (**338**, 0.17 mL, 1.1 mmol) in diethyl ether (1 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (**329**, 0.15 g, 1.1 mmol) and triethylamine (0.16 mL, 1.1 mmol) in dichloromethane (8 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 3.4 mL) were also transferred to the flask containing 3-phenyl-2-propyn-1-ol and triethylamine. The reaction mixture was stirred at 0 °C for 40 minutes followed by stirring at rt overnight under argon.

The reaction mixture was quenched with sat. aqueous NH_4Cl (15 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, hexane / Et_3N 99 : 1) afforded allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**327b**, 0.20 g, 50%) as a colourless oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3071s (=C-H$_2$), 2972m & 2862m (C-H), 2150w (C≡C), 1630s (C=C), 1589m (C=C aromatic), 1489s (C=C aromatic), 1443m, 1429m, 1371s; δ_H (500 MHz; $CDCl_3$) 7.68-7.66 (4H, m, arom.*H*), 7.44-7.29 (11H, m, arom.*H*), 5.90 (1H, ddt, *J* 18.0, 10.1, 7.9, *H*C=CH$_2$), 4.99 (1H, ddt, *J* 17.0, 1.9, 1.5, 1 of HC=C*H*$_2$ (*trans*)), 4.92

(1H, ddt, *J* 10.1, 1.9, 1.0, 1 of HC=CH_2 (*cis*)), 4.63 (2H, s, OCH_2), 2.30 (2H, dt, *J* 7.9, 1.2, SiCH_2); δ_C (75 MHz; $CDCl_3$) 134.9 (arom.*C*H), 133.9 (arom.C_q), 132.7 (*H*C=CH_2), 131.6 (arom.*C*H), 130.1 (arom.*C*H), 128.3 (arom.*C*H), 128.2 (arom.*C*H), 127.9 (arom.*C*H), 122.8 (arom.C_q), 115.4 (C=CH_2), 87.3 & 85.6 (*C*≡*C*), 52.8 (OCH_2), 22.0 ($SiCH_2$); *m/z* (FAB pos) 377 (MNa^+, 2%), 338 (9), 313 (35), 283 (100) 199 (41); HRMS calculated for $C_{24}H_{22}OSiNa$ (MNa^+) 377.1338 Found 377.1334.

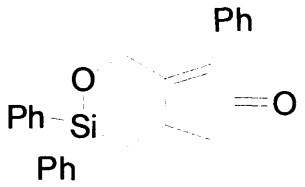
Synthesis of Dicobalt hexacarbonyl complex of Allyldiphenyl(3-phenylprop-2-ynyloxy)silane 331b



Using the procedure of Mukai *et al.*[91], a solution of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**327b**, 0.58 g, 1.6 mmol) in dichloromethane (6 mL) was added to a solution of dicobalt octacarbonyl (0.76 g, 2.2 mmol) in dichloromethane (7 mL) under argon at rt. The resulting reaction mixture was stirred at rt for 6 h. The reaction mixture was concentrated *in vacuo* at rt and the residue was purified by flash chromatography (Florisil®, hexane / Ether 100 : 0 to 99 : 1) to afford dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.97 g, 93%) as a deep red oil.

ν_{max} (neat)/cm^{-1} 3072s (=C-H_2), 3055s (C-H), 2091s & 2016s (Co-C≡O), 1632s (C=C), 1575m (C=C aromatic), 1483m (C=C aromatic), 1443m, 1429s, 1356m; δ_H (400 MHz; $CDCl_3$) 7.67(4H, br m, arom.*H*), 7.50-7.30 (11H, br m, arom.*H*), 5.88 (1H, br m, *H*C=CH_2), 5.12 (2H, s, OCH_2), 4.99 (1H, br d, *J* 16.9, HC=CH_2 (*trans*)), 4.93 (1H br d, *J* 9.9 HC=CH_2 (*cis*)), 2.28 (2H, br d, *J* 7.7, SiCH_2); δ_C (100 MHz; $CDCl_3$ + $Cr(acac)_3$) 199.3 (*C*=O), 137.7 (arom.C_q), 134.8 (arom.*C*H), 133.6 (arom.C_q), 132.6 (*H*C=CH_2), 130.2 (arom.*C*H), 129.7 (arom.*C*H), 128.8 (arom.*C*H), 127.9 (arom.*C*H), 127.8 (arom.*C*H), 115.4 (HC=CH_2), 96.0 & 90.1 ($(OC)_3Co$*C*-*C*$Co(CO)_3$), 64.4 (OCH_2), 21.6 ($SiCH_2$); *m/z* (CI Pos) 641 (MH^+, 3%), 556, (63), 472 (45), 401 (100); HRMS calculated for $C_{30}H_{23}O_7SiCo_2$ (MH^+) 640.9877 Found 640.9896.

Synthesis of 3,3,7-Triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328b



Method 1

A solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.16 g, 0.25 mmol) in toluene (2.5 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, hexane / Ether 7 : 3) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328b**, 27 mg, 28%) as a white foam.

Method 2

Using the procedure of Mukai *et al.*[91], a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.13 g, 0.2 mmol) in acetonitrile (0.8 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / Ether 3 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328b**, 27 mg, 35%) as a white foam.

Method 3

Using the procedure of Pagenkopf *et al.*[86], a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.13 g, 0.20 mmol) and H_2O (8.1 µL, 0.44 mmol) in acetonitrile (0.8 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / Ether 3 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328b**, 37 mg, 48%) as a white foam.

Method 4

Using the procedure of Perez-Castells *et al.*[34], a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.14 g, 0.22 mmol) in

toluene (8.7 mL) containing activated 4Å molecular sieve powder (1.12 g), was stirred at rt under argon for 1 h. The reaction mixture was heated to reflux under argon for 4.5 h,then cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / Ether 7 : 3) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328b**, 13 mg, 15%) as a white foam.

Method 5

Using the procedure of Schreiber *et al.*[25], a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.14 g, 0.22 mmol) in dichloromethane (40 mL) under argon was treated with a single portion of 4-methylmorpholine-*N*-oxide monohydrate (0.18 g, 1.3 mmol). The resulting reaction mixture was stirred at rt overnight, then concentrated *in vacuo* and purified by flash chromatography (SiO_2, Petrol 40-60 / Ether 4 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328b**, 37 mg, 45%) as a white foam.

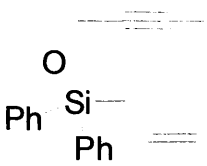
Method 6

Using the procedure of Sugihara *et al.*[29], a solution of dicobalt hexacarbonyl complex of allyldiphenyl(3-phenylprop-2-ynyloxy)silane (**331b**, 0.16 g, 0.24 mmol) and *n*-butyl methyl sulfide (0.11 mL, 0.85 mmol) in 1,2-dichloroethane (2.44 mL) was heated to reflux under argon overnight. The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / Ether 3 : 1) to afford 3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328b**, 65 mg, 70%) as a white foam.

m.p.: 59 °C; ν_{max} (KBr)/cm^{-1} 2924s & 2853m (C-H), 1701s (C=O), 1429m (C=C aromatic), 1105s; δ_H (500 MHz; $CDCl_3$) 7.73-7.71 (2H, m, arom.*H*), 7.54-7.52 (2H, m, arom.*H*), 7.47-7.46 (3H, m, arom.*H*), 7.41-7.35 (6H, m, arom.*H*), 7.25-7.23 (2H, m, arom.*H*), 5.15 (1H, d, *J* 16.2, 1 of OCH_2), 4.98 (1H, d, *J* 16.2, 1 of OCH_2), 3.34-3.31 (1H, m, $SiCH_2CH$), 2.94 (1H, dd, *J* 18.9, 6.5, 1 of $OCCH_2$), 2.34 (1H, dd, *J* 18.9, 2.1, 1 of $OCCH_2$), 1.90 (1H, dd, *J* 14.6, 4.9, 1 of $SiCH_2$), 1.24 (1H, dd, *J* 14.5, 13.7, 1 of $SiCH_2$); δ_C (125 MHz; $CDCl_3$) 205.7 (*C*=O), 172.1 (OCH_2C=C), 138.5(C=*C*Ph), 134.3 (arom.*C*H), 134.2 (arom.*C*H), 133.8 (arom.C_q), 133.5 (arom.C_q), 130.6 (arom.*C*H), 130.54 (arom.*C*H), 130.49 (arom.C_q), 129.0 (arom.*C*H), 128.4 (arom.*C*H), 128.3

(arom.*C*H), 128.2 (arom.*C*H), 128.1 (arom.*C*H), 63.2 (O*C*H_2), 45.8 (OC*C*H_2), 35.6 (SiCH_2*C*H), 19.2 (Si*C*H_2); *m/z* (FAB pos) 383 (MH^+, 15%), 338 (100), 307 (30); HRMS calculated for $C_{25}H_{23}O_2Si$ (MH^+) 383.1467 Found 383.1472.

Synthesis of Allyldiphenylprop-2-ynyloxysilane 327c



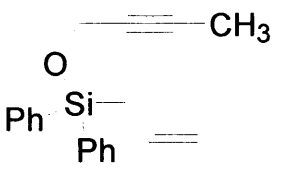
Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 4.6 mL, 4.6 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (**338**, 0.33 mL, 2.3 mmol) in diethyl ether (2 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt, diluted with dichloromethane (3.8 mL) and added dropwise to a solution of propargyl alcohol (**256**, 0.13 g, 2.3 mmol) and triethylamine (0.32 mL, 2.3 mmol) in dichloromethane (19 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 2 mL) were transferred to the flask containing propargyl alcohol and triethylamine. The reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (15 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (120 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60) afforded allyldiphenylprop-2-ynyloxysilane (**327c**, 0.11 g, 18%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3292s (C≡C-H), 3025s (=C-H_2), 2999m & 2866m (C-H), 2100w (C≡C), 1630s (C=C), 1589m (C=C aromatic), 1487w (C=C aromatic), 1429s, 1371m, 1263m; δ_H (500 MHz; $CDCl_3$) 7.65-7.63 (4H, m, arom.*H*), 7.47-7.38 (6H, m, arom.*H*), 5.87 (1H, ddt, *J* 17.0, 10.1, 7.9, *H*C=CH_2), 4.99 (1H, ddt, *J* 17.0, 1.9, 1.5, 1 of HC=CH_2 (*trans*)), 4.93 (1H, ddt, *J* 10.1, 1.9, 1.1, 1 of HC=CH_2 (*cis*)), 4.39 (2H, d, *J* 2.4, OCH_2), 2.41 (1H, t, *J* 2.4, C≡C-*H*), 2.26 (2H, dt, *J* 7.9, 1.3, SiCH_2); δ_C (100 MHz; $CDCl_3$) 134.8 (arom.*C*H), 133.5 (arom.C_q), 132.6 (H*C*=CH_2), 130.2 (arom.*C*H), 127.9 (arom.*C*H), 115.4 (HC=*C*H_2), 81.7 (*C*≡C-H), 73.5 (C≡*C*-H), 52.0 (O*C*H_2), 21.8

($SiCH_2$); *m/z* (FAB pos) 360 (100%), 301 (MNa^+, 10), 237 (28), 207 (75); HRMS calculated for $C_{18}H_{18}OSiNa$ (MNa^+) 301.1025 Found 301.1020.

Synthesis of Allylbut-2-ynyloxydiphenylsilane 327d

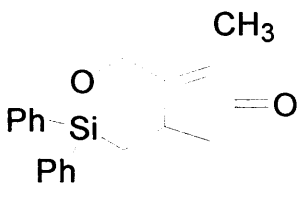


Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 4.6 mL, 4.6 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (**338**, 0.33 mL, 2.3 mmol) in diethyl ether (2 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt and added dropwise to a solution of but-2-yn-1-ol (0.16 g, 2.3 mmol) and triethylamine (0.32 mL, 2.3 mmol) in dichloromethane (19 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 3.8 mL) were transferred to the flask containing but-2-yn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (120 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, hexane / Et_3N 99 : 1) afforded allylbut-2-ynyloxydiphenylsilane (**327d**, 0.22 g, 32%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3071s (=C-H_2), 2999m & 2866m (C-H), 2235w (C≡C), 1630s (C=C), 1589m (C=C aromatic), 1487w (C=C aromatic), 1429s, 1371m; δ_H (500 MHz; $CDCl_3$) 7.65-7.63 (4H, m, arom.*H*), 7.45-7.38 (6H, m, arom.*H*), 5.88 (1H, ddt, *J* 17.0, 10.1, 7.9, *H*C=CH_2), 4.98 (1H, ddt, *J* 17.0, 1.9, 1.5, 1 of HC=CH_2 (*trans*)), 4.92 (1H, ddt, *J* 10.1, 2.0, 1.1, 1 of HC=CH_2 (*cis*)), 4.37 (2H, q, *J* 2.4, OCH_2), 2.26 (2H, dt, *J* 7.9, 1.3, SiCH_2), 1.80 (3H, t, *J* 2.4, CH_3); δ_C (100 MHz; $CDCl_3$) 134.8 (arom.*C*H), 133.9 (arom.C_q), 132.8 (H*C*=CH_2), 130.0 (arom.*C*H), 127.8 (arom.*C*H), 115.2 (HC=*C*H_2), 81.8 (OCH_2C≡C), 77.2 (C≡*C*CH_3), 52.5 (OCH_2), 21.9 ($SiCH_2$), 3.6 (CH_3); *m/z* (FAB pos) 315 (MNa^+, 29%), 251 (35), 221 (100); HRMS calculated for $C_{19}H_{20}OSiNa$ (MNa^+) 315.1181 Found 315.1182.

Synthesis of 7-Methyl-3,3-diphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328d

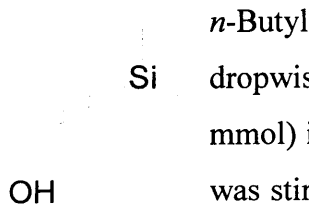


Using the procedure of Sugihara *et al.*[29], a solution of allylbut-2-ynyloxydiphenylsilane (**327d**, 0.16 g, 0.55 mmol) in 1,2-dichloroethane (3.5 mL) was added to a solution of dicobalt octacarbonyl (0.40 g, 1.2 mmol) in 1,2-dichloroethane (2 mL) under argon at rt. The reaction mixture was stirred at rt for 85 minutes. *n*-Butyl methyl sulfide (0.24 mL, 1.93 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (Florisil®, Dichloromethane) to afford 7-methyl-3,3-diphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328d**, 67 mg, 38%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 2922m & 2853w (C-H), 1701s (C=O), 1647s (C=C), 1589m (C=C aromatic), 1429s, 1408s, 1380w; δ_H (500 MHz; $CDCl_3$) 7.72-7.70 (2H, m, arom.*H*), 7.55-7.54 (2H, m, arom.*H*), 7.49-7.43 (4H, m, arom.*H*), 7.41-7.36 (2H, m, arom.*H*), 5.07 (1H, d, *J* 16.2, 1 of OCH_2), 4.86 (1H, d, *J* 16.2, 1 of OCH_2), 3.15-3.09 (1H, m, SiCH$_2$C*H*), 2.79 (1H, dd, *J* 18.8, 6.3, 1 of OCCH_2), 2.16 (1H, dd, *J* 18.8, 1.5, 1 of OCCH_2), 1.81 (1H, dd, *J* 14.5, 4.8, 1 of SiCH_2), 1.70 (3H, br s, CH_3), 1.21 (1H, t, *J* 14.3, 1 of SiCH_2); δ_C (125 MHz; $CDCl_3$) 207.9 (*C*=O), 170.6 (*C*=CCH$_3$) & 134.5 (C=*C*CH$_3$), 134.2 (arom.*C*H) , 134.1 (arom.*C*H), 134.0 (arom.C_q), 133.6 (arom.C_q), 130.5 (arom.*C*H), 130.4 (arom.*C*H), 128.2 (arom.*C*H), 128.1 (arom.*C*H), 62.8 (OCH$_2$), 45.1 (OCCH$_2$), 35.3 (SiCH$_2$CH), 18.8 (SiCH$_2$), 7.7 (CH$_3$); *m/z* (FAB pos) 321 (MH$^+$, 25%) , 307 (40), 289 (18), 154 (100); HRMS calculated for $C_{20}H_{21}O_2Si$ (MH$^+$) 321.1311 Found 321.1303.

Synthesis of 3-Trimethylsilanylprop-2-yn-1-ol 340[97]

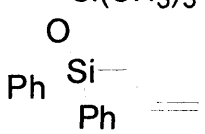


n-Butyllithium (1.6 M in hexane, 44.6 mL, 71.4 mmol) was added dropwise to a stirred solution of propargyl alcohol (**256**, 2.11 mL, 35.7 mmol) in THF (150 mL) at –78 °C under argon and the reaction mixture was stirred at –78 °C for 1 h. Chlorotrimethylsilane (9.1 mL, 71 mmol) was added dropwise and the resulting reaction mixture was stirred at –78 °C for 30 minutes followed by stirring at rt overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (25 mL) and THF removed *in vacuo* at rt. The residue was extracted with diethyl ether (3 x 75 mL). The combined ethereal extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Et_3N / Ether / Petrol 40-60 0.5 : 0 : 99.5 to 0.5 : 15 : 84.5) afforded 3-trimethylsilanylprop-2-yn-1-ol (**340**, 3.66 g, 80%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 3306 br s (O-H), 2959s (C-H), 2176s (C≡C), 1410s, 1352s; δ_H (500 MHz; $CDCl_3$) 4.23 (2H, s, OCH_2), 2.57 (1H, br s, OH), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (125 MHz; $CDCl_3$) 103.9 (C≡$CSi(CH_3)_3$), 90.4 (C≡$CSi(CH_3)_3$), 51.3 (OCH_2), –0.3 ($Si(CH_3)_3$); *m/z* (CI pos) 129 (MH^+, 26%), 113 (100), 100 (20); HRMS calculated for $C_6H_{13}OSi$ (MH^+) 129.0736 Found 129.0742.

Synthesis of 1-Allyl-3,3,3-trimethyl-1,1-diphenyldisiloxane 341



Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 3.4 mL, 3.4 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (**338**, 0.25 mL, 1.7 mmol) in diethyl ether (1.5 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 1 h, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt and added dropwise to a solution of propargyl alcohol (**256**, 0.10 g, 1.7 mmol) and triethylamine (0.24 mL, 1.7 mmol) in dichloromethane (17 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 2 mL) were transferred to the flask containing propargyl alcohol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt overnight under argon. The reaction mixture was quenched with sat. aqueous NH_4Cl (10 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude allyldiphenylprop-2-ynyloxysilane (**327c**, 0.45 g).

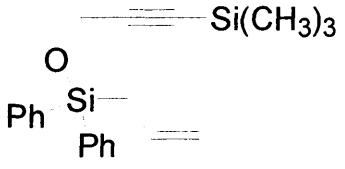
Lithium (bistrimethyl)silylamide (1.2 M in THF, 0.33 mL, 0.4 mmol) was added dropwise to a stirred solution of crude allyldiphenylprop-2-ynyloxysilane (**327c**, 0.10 g, 0.4 mmol) in THF (1 mL) at -78 °C under argon. The reaction mixture was stirred at –78 °C for 130 minutes. Chlorotrimethylsilane (43 mg, 50 μL, 0.4 mmol) was added

dropwise and the resulting reaction mixture was stirred at –78 °C for 30 minutes followed by stirring at rt overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (1 mL) and extracted with diethyl ether (4 x 10 mL). The combined ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Al_2O_3, Petrol 40-60) afforded 1-allyl-3,3,3-trimethyl-1,1-diphenyldisiloxane (**341**, 28 mg, 25%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3071s (=C-H_2), 2957s & 2916m (C-H), 1630s (C=C), 1591m (C=C aromatic), 1487w (C=C aromatic), 1429s, 1418m, 1389m; δ_H (500 MHz; $CDCl_3$) 7.58-7.56 (4H, m, arom.*H*), 7.41-7.36 (6H, m, arom.*H*), 5.82 (1H, ddt, *J* 17.0, 10.1, 7.9, *H*C=CH_2), 4.94 (1H, ddt, *J* 17.0, 2.1, 1.5, 1 of HC=CH_2 (*trans*)), 4.90 (1H, ddt, *J* 10.1, 2.1, 1.1, 1 of HC=CH_2 (*cis*)), 2.12 (2H, dt, *J* 7.9, 1.2, SiCH_2), 0.13 (9H, s, Si(CH_3)$_3$); δ_C (125 MHz; $CDCl_3$) 136.6 (arom.C_q), 134.2 (arom.*C*H), 133.3 (H*C*=CH_2), 129.6 (arom.*C*H), 127.7 (arom.*C*H), 114.7 (HC=*C*H_2), 23.8 (Si*C*H_2), 2.0 (Si(*C*H_3)$_3$); *m/z* (FAB pos) 313 (MH^+, 2%), 297 (30), 271 (100), 235 (65), 178 (15), 79 (20).

Synthesis of Allyldiphenyl(3-trimethylsilanylprop-2-ynyloxy)silane 327e



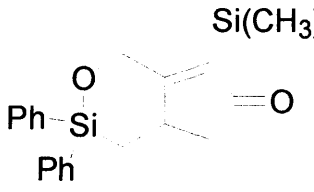
Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 5.7 mL, 5.7 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (**338**, 0.41 mL, 2.9 mmol) in diethyl ether (2.4 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt and added dropwise to a solution of 3-trimethylsilanylprop-2-yn-1-ol (**340**, 0.37 g, 2.9 mmol), 4-dimethylaminopyridine (35 mg, 0.28 mmol) and triethylamine (0.40 mL, 2.9 mmol) in dichloromethane (28.5 mL) under argon at –78 °C. The reaction mixture was stirred at –78 °C for 1 h, followed by stirring at rt for 2 days.

The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL) and extracted with dichloromethane (3 x 60 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 99.75 : 0.25) afforded

allyldiphenyl(3-trimethylsilanylprop-2-ynyloxy)silane (**327e**, 0.29 g, 29%) as a pale yellow oil.

ν_{max} (neat)/cm^{-1} 3071s (=C-H$_2$), 2961s & 2860m (C-H), 2179m (C≡C), 1630s (C=C), 1589m (C=C aromatic), 1489m (C=C aromatic), 1452m, 1429s, 1389m; δ_H (500 MHz; $CDCl_3$) 7.67-7.65 (4H, m, arom.*H*), 7.46-7.38 (6H, m, arom.*H*), 5.89 (1H, ddt, *J* 17.0, 10.1, 7.9, *H*C=CH$_2$), 4.99 (1H, ddt, *J* 17.0, 2.0, 1.5, 1 of HC=C*H*$_2$ (*trans*)), 4.93 (1H, ddt, *J* 10.1, 2.0, 1.1, 1 of HC=C*H*$_2$ (*cis*)), 4.41 (2H, s, OC*H*$_2$), 2.28 (2H, dt, *J* 7.8, 1.3, SiC*H*$_2$), 0.17 (9H, s, Si(C*H*$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 134.9 (arom.*C*H), 133.8 (arom.*C*$_q$), 132.8 (H*C*=CH$_2$), 130.1 (arom.*C*H), 127.8 (arom.*C*H), 115.3 (HC=*C*H$_2$), 103.7 (*C*≡CSi(CH$_3$)$_3$), 90.5 (C≡*C*Si(CH$_3$)$_3$), 52.8 (O*C*H$_2$), 22.0 (Si*C*H$_2$), -0.3 (Si(*C*H$_3$)$_3$); *m/z* (FAB pos) 373 (MNa$^+$, 30%) , 209 (15), 279 (100); HRMS calculated for $C_{21}H_{26}OSi_2Na$ (MNa$^+$) 373.1420 Found 373.1424.

Synthesis of 3,3-Diphenyl-7-trimethylsilanyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328e



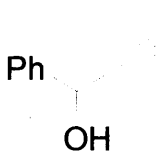
Using the procedure of Sugihara *et al.*[29], a solution of allyldiphenyl(3-trimethylsilanylprop-2-ynyloxy)silane (**327e**, 0.12 g, 0.34 mmol) in 1,2-dichloroethane (1.9 mL) was added to a solution of dicobalt octacarbonyl (0.18 g, 0.51 mmol) in 1,2-dichloroethane (1.5 mL) under argon at rt. The reaction mixture was stirred at rt for 1 h. *n*-Butyl methyl sulfide (0.15 mL, 1.2 mmol) was added and the resulting reaction mixture was heated to reflux for 3 days.

The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 7 : 3) to afford 3,3-diphenyl-7-trimethylsilanyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328e**, 18 mg, 14%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 2955m & 2899m (C-H), 1690 br s (C=O), 1589s (C=C aromatic), 1429s, 1406m, 1250s; δ_H (500 MHz; $CDCl_3$) 7.69-7.68 (2H, m, arom.*H*), 7.57-7.56 (2H, m, arom.*H*), 7.49-7.35 (6H, m, arom.*H*), 5.12 (1H, d, *J* 17.1, 1 of OC*H*$_2$), 4.98 (1H, d, *J* 17.1, 1 of OC*H*$_2$), 3.30-3.23 (1H, m, SiCH$_2$C*H*), 2.75 (1H, dd, *J* 18.5, 6.0, 1 of OCC*H*$_2$), 2.13 (1H, dd, *J* 18.6, 2.5, 1 of OCC*H*$_2$), 1.80 (1H, dd, *J* 14.7, 4.9, 1 of SiC*H*$_2$), 1.19 (1H,

t, *J* 14.4, 1 of $SiCH_2$), 0.21 (9H, s, $Si(CH_3)_3$); δ_C (125 MHz; $CDCl_3$) 211.7 (*C*=O), 187.1 (*C*=$CSi(CH_3)_3$), 138.1 (C=*C*$Si(CH_3)_3$), 134.22 (arom.*C*H), 134.21 (arom.*C*H), 134.0 (arom.C_q), 133.7 (arom.C_q), 130.6 (arom.*C*H), 130.5 (arom.*C*H), 128.2 (arom.*C*H), 128.1 (arom.*C*H), 64.6 (OCH_2), 46.2 ($OCCH_2$), 38.5 ($SiCH_2CH$), 18.4 ($SiCH_2$), -0.6 ($Si(CH_3)_3$); *m/z* (CI pos) 379 (MH^+, 11%), 363 (15), 309 (70), 273 (85), 199 (100), 163 (80); HRMS calculated for $C_{22}H_{27}O_2Si_2$ (MH^+) 379.1550 Found 379.1560.

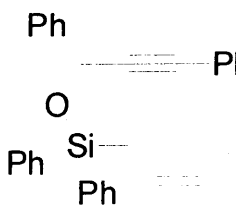
Synthesis of 1,3-Diphenylprop-2yn-1-ol 343[98]



n-Butyllithium (1.6 M in hexane, 6.2 mL, 9.9 mmol) was added dropwise to a stirred solution of phenylacetylene (**16**, 1.1 mL, 9.8 mmol) in THF (6.5 mL) at –78 °C, under argon, and stirred for 10 minutes. Benzaldehyde (**342**, 1.0 mL, 9.8 mmol) was added dropwise and the resulting reaction mixture stirred at –78 °C for 10 minutes followed by stirring at rt overnight.
The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL) and extracted with diethyl ether (2 x 100 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Petrol 40-60 / EtOAc 85 : 15) afforded 1,3-diphenylprop-2yn-1-ol (**343**, 1.8 g, 90%) as a pale yellow oil.

ν_{max} (neat)/cm^{-1} 3346 br s (O-H), 3063m (C-H), 2199m (C≡C), 1597m (C=C aromatic), 1489s (C=C aromatic), 1443s, 1387m, 1286m; δ_H (300 MHz; $CDCl_3$) 7.66-7.64 (2H, m, arom.*H*), 7.53-7.50 (2H, m, arom.*H*), 7.45-7.33 (6H, m, arom.*H*), 5.71 (1H, s, HOC*H*), 2.94 (1H, br s, O*H*); δ_C (75 MHz; $CDCl_3$) 140.5 (arom.C_q), 131.7 (arom.*C*H), 128.54 (arom.*C*H), 128.48 (arom.*C*H), 128.3 (arom.*C*H), 128.2 (arom.*C*H), 126.7 (arom.*C*H), 122.3 (arom.C_q), 88.7 & 86.5 (*C*≡*C*), 64.9 (HO*C*H); *m/z* (FAB pos) 208 (M^+, 5%), 191 (25), 154 (100), 136 (70), 77 (40); HRMS calculated for $C_{15}H_{12}O$ (M^+) 208.0888 Found 208.0882

Synthesis of Allyl(1,3-diphenylprop-2-ynyloxy)diphenylsilane 327f



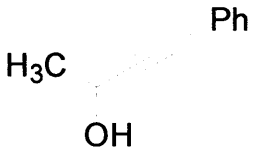
Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 6.8 mL, 6.8 mmol) was added dropwise to a stirred solution of allyltrichlorosilane (**338**, 0.50 mL, 3.4 mmol) in diethyl ether (3 mL) at –78 °C under argon.

The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt and added dropwise to a solution of 1,3-diphenylprop-2yn-1-ol (**343**, 0.71 g, 3.4 mmol), 4-dimethylaminopyridine (42 mg, 0.34 mmol) and triethylamine (0.48 mL, 3.4 mmol) in dichloromethane (30 mL) under argon at 0 °C. The washings from the flask containing allylchlorodiphenylsilane (dichloromethane, 4.2 mL) were transferred to the flask containing 1,3-diphenylprop-2yn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon overnight.

The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (4 x 75 mL). The combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Al_2O_3, Petrol 40-60) afforded allyl(1,3-diphenylprop-2-ynyloxy)diphenylsilane (**327f**, 0.69 g, 47%) as a thick yellow oil.

ν_{max} (neat)/cm^{-1} 3070s (=C-H$_2$), 3027s (C-H), 2200w (C≡C), 1685m (C=C aromatic), 1630m (C=C), 1599m (C=C aromatic), 1490m (C=C aromatic), 1450m, 1443m, 1428s; δ_H (500 MHz; $CDCl_3$) 7.74-7.70 (4H, m, arom.*H*), 7.59-7.57 (2H, m, arom.*H*), 7.48-7.44 (2H, m, arom.*H*), 7.42-7.38 (6H, m, arom.*H*), 7.36-7.28 (6H, m, arom.*H*), 5.92 (1H, ddt, *J* 17.0, 10.1, 8.0, *H*C=CH$_2$), 5.81 (1H, s, OC*H*), 4.99 (1H, ddt, *J* 17.0, 2.0, 1.4, 1 of HC=C*H*$_2$ (*trans*)), 4.93 (1H, ddt, *J* 10.1, 2.1, 1.0, 1 of HC=C*H*$_2$ (*cis*)), 2.39 (1H, ddt, *J* 14.1, 7.7, 1.3, 1 of SiC*H*$_2$), 2.35 (1H, ddt, *J* 14.1, 8.1, 1.3, 1 of SiC*H*$_2$); δ_C (125 MHz; $CDCl_3$) 141.1 (arom.C_q), 135.05 (arom.*C*H), 135.0 (arom.*C*H), 134.2 (arom.C_q), 134.1 (arom.C_q), 132.9 (H*C*=CH$_2$), 131.6 (arom.*C*H), 130.04 (arom.*C*H), 130.0 (arom.*C*H), 128.4 (arom.*C*H), 128.3 (arom.*C*H), 128.1 (arom.*C*H), 127.9 (arom.*C*H), 127.8 (arom.*C*H), 127.7 (arom.*C*H), 126.5 (arom.*C*H), 122.6 (arom.C_q), 115.3 (HC=*C*H$_2$), 89.5 & 86.5 (*C*≡*C*), 65.9 (OCH), 22.3 (SiCH$_2$); *m/z* (FAB pos) 453 (MNa$^+$, 1%), 389 (15), 283 (35), 191 (100); HRMS calculated for $C_{30}H_{26}OSiNa$ (MNa$^+$) 453.1651 Found 453.1661.

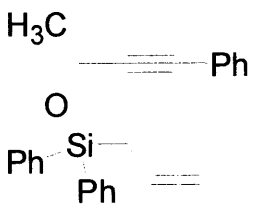
Synthesis of 4-Phenylbut-3-yn-2-ol 345[98]



n-Butyllithium (1.6 M in hexane, 9.27 mL, 14.83 mmol) was added dropwise to a stirred solution of phenylacetylene (**16**, 1.61 mL, 14.7 mmol) in THF (10 mL) at –78 °C under argon and stirred for 15 minutes. Acetaldehyde (**344**, 0.82 mL, 14.7 mmol) was added dropwise and resulting reaction mixture stirred at –78 °C for 30 minutes followed by stirring at rt overnight. The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL) and extracted with diethyl ether (2 x 100 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Petrol 40-60 / EtOAc 9 : 15) afforded 4-phenylbut-3-yn-2-ol (**345**, 1.4 g, 64%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 3320 br s (O-H), 2981s (C-H), 2150w (C≡C), 1598s (C=C aromatic), 1490s (C=C aromatic), 1443s, 1370s, 1330s; δ_H (400 MHz; $CDCl_3$) 7.44-7.41 (2H, m, arom.*H*), 7.31-7.29 (3H, m, arom.*H*), 4.76 (1H, q, *J* 6.6, HOC*H*), 2.36 (1H, br s, O*H*), 1.55 (3H, d, *J* 6.6, CH_3); δ_C (100 MHz; $CDCl_3$) 131.6 (arom.*C*H), 128.3 (arom.*C*H), 128.2 (arom.*C*H), 122.5 (arom.C_q), 90.9 (C≡*C*Ph), 83.9 (*C*≡CPh), 58.7 (HO*C*H), 24.3 (CH_3) ; *m/z* (CI pos) 147 (MH^+, 22%), 129 (100), 103 (20); HRMS calculated for $C_{10}H_{11}O$ (MH^+) 147.0810 Found 147.0804.

Synthesis of Allyldiphenyl(4-phenylbut-3-yn-2-yloxy)silane 327g

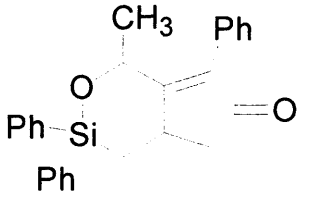


Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 6.8 mL, 6.8 mmol) was added to a stirred solution of allyltrichlorosilane (**338**, 0.50 mL, 3.4 mmol) in diethyl ether (3 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain allylchlorodiphenylsilane (**330b**) in solution. This solution was cooled to rt, diluted with dichloromethane (4.2 mL) and added dropwise to a solution of 4-phenylbut-3-yn-2-ol (**345**, 0.50 g, 3.4 mmol), 4-dimethylaminopyridine (42 mg, 0.34 mmol) and triethylamine (0.48 mL, 3.4 mmol) in dichloromethane (30 mL) under argon at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt, under argon for 3 days.

The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 75 mL). The combined organic extracts were washed with brine (120 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Al_2O_3, Petrol 40-60) afforded allyldiphenyl(4-phenylbut-3-yn-2-yloxy)silane (**327g**, 0.79g, 63%) as a light yellow oil.

ν_{max} (neat)/cm^{-1} 3070m (=C-H_2), 2999m (C-H), 2200w (C≡C), 1630m (C=C), 1590w (C=C aromatic), 1490s (C=C aromatic), 1428s, 1325w; δ_H (500 MHz; $CDCl_3$) 7.75-7.73 (4H, m, arom.*H*), 7.49-7.41 (6H, m, arom.*H*), 7.35-7.30 (5H, m, arom.*H*), 5.97 (1H, ddt, *J* 17.0, 10.1, 7.9, *H*C=CH_2), 5.04 (1H, ddt, *J* 17.0, 2.0, 1.5, 1 of HC=CH_2 (*trans*)), 4.97 (1H, ddt, *J* 10.1, 2.0, 1.0, 1 of HC=CH_2 (*cis*)), 4.89 (1H, q, *J* 6.5, OC*H*), 2.37-2.36 (2H, m, SiCH_2), 1.61 (3H, d, *J* 6.5, CH_3); δ_C (125 MHz; $CDCl_3$) 134.93 (arom.*C*H), 134.91 (arom.*C*H), 134.40 (arom.C_q), 134.38 (arom.C_q), 133.0 (*H*C=CH_2), 131.5 (arom.*C*H), 129.94 (arom.*C*H), 129.91 (arom.*C*H), 128.1 (arom.*C*H), 127.8 (arom.*C*H), 127.7 (arom.*C*H), 122.8 (arom.C_q), 115.2 (HC=CH_2), 91.2 & 84.1 (*C*≡*C*), 60.2 (O*C*H), 25.2 (CH_3), 22.3 ($SiCH_2$); *m/z* (FAB pos) 369 (MH^+, 4%), 327 (100), 291 (70), 267 (60), 129 (90) ; HRMS calculated for $C_{25}H_{25}OSi$ (MH^+) 369.1675 Found 369.1672.

Synthesis of 5-Methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328g



Using the procedure of Sugihara *et a.l*[29], a solution of allyldiphenyl(4-phenylbut-3-yn-2-yloxy)silane (**327g**, 0.15 g, 0.41 mmol) in 1,2-dichloroethane (2.5 mL) was added to a solution of dicobalt octacarbonyl (0.17 g, 0.49 mmol) in 1,2-dichloroethane (1.6 mL) under argon at rt. The reaction mixture was stirred at rt for 1 h. *n*-Butyl methyl sulfide (0.18 mL, 1.4 mmol) was added and the reaction mixture was heated to reflux under argon overnight.

The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / EtOAc 85 : 15) to afford 5-methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (**328g**, 15 mg, 9%) as an inseparable mixture of *endo:exo* diastereoisomers in the ratio of 1:1.5.

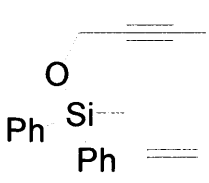
ν_{max} (neat)/cm^{-1} 2925s (C-H), 1710s (C=O), 1699s (C=C), 1682m (C=C aromatic), 1428s (C=C aromatic), 1278w, 1120s, 1071s; δ_H (500 MHz; $CDCl_3$, major isomer) 7.74-7.72 (2H, m, arom.*H*), 7.53-7.51 (2H, m, arom.*H*), 7.48-7.30 (9H, m, arom.*H*), 7.20-7.18 (2H, m, arom.*H*), 5.42 (1H, q, *J* 6.6, OC*H*), 3.46-3.42 (1H, m, $SiCH_2CH$), 2.95 (1H, dd, *J* 18.9, 6.5, 1 of $OCCH_2$), 2.35 (1H, dd, *J* 18.9, 1.7, 1 of $OCCH_2$), 1.98 (1H, dd, *J* 14.7, 5.2, 1 of $SiCH_2$), 1.40 (3H, d, *J* 6.7, CH_3), 1.22 (1H, dd, *J* 14.7, 13.3, 1 of $SiCH_2$); δ_H (500 MHz; $CDCl_3$, minor isomer) 7.68-7.66 (2H, m, arom.*H*), 7.62-7.60 (2H, m, arom.*H*), 7.48-7.30 (9H, m, arom.*H*), 7.22-7.21 (2H, m, arom.*H*), 5.63 (1H, qt, *J* 6.9, 1.1, OC*H*), 3.46-3.42 (1H, m, $SiCH_2CH$), 2.96 (1H, ddd, *J* 18.9, 6.5, 1.2, 1 of $OCCH_2$) , 2.34 (1H, dd, *J* 18.8, 2.8, 1 of $OCCH_2$), 1.77 (1H, dd, *J* 14.7, 4.0, 1 of $SiCH_2$), 1.36 (1H, t, *J* 14.5, 1 of $SiCH_2$), 1.13 (3H, d, *J* 6.7, CH_3); δ_C (125 MHz; $CDCl_3$) 206.3 (*C*=O major), 205.7 (*C*=O minor), 179.0 (*C*=CPh minor), 176.8 (*C*=CPh major), 138.5 (C=*C*Ph minor), 138.3 (C=*C*Ph major), 135.7 (arom.C_q minor), 135.0 (arom.C_q major), 134.9 (arom.C_q major), 134.6 (arom.C_q minor), 134.3 (arom.*C*H minor), 134.21 (arom.*C*H major), 134.18 (arom.*C*H major), 134.0 (arom.*C*H minor), 131.9 (C=Carom.C_q minor), 131.0 (C=Carom.C_q major), 130.4 (arom.*C*H), 130.32 (arom.*C*H), 130.30 (arom.*C*H), 128.8 (C=Carom.*C*H major), 128.62 (C=Carom.*C*H minor), 128.6 (arom.*C*H), 128.5 (arom.*C*H), 128.11 (arom.*C*H), 128.08 (arom.*C*H), 128.05 (arom.*C*H), 128.03 (arom.*C*H), 127.99 (arom.*C*H), 70.9 (O*C*H minor), 69.1 (O*C*H major), 45.7 (O*C*CH_2 major), 45.3 (O*C*CH_2 minor), 35.7 ($SiCH_2CH$ minor), 32.7 ($SiCH_2CH$ major), 23.9 (CH_3 minor), 23.4 (CH_3 major), 20.3 ($SiCH_2$ major), 16.6 ($SiCH_2$ minor); *m/z* (CI pos) 397 (MH^+, 100%), 319 (38), 199 (35); HRMS calculated for $C_{26}H_{25}O_2Si$ (MH^+) 397.1624 Found 397.1631.

Synthesis of Trichloro(2-methylallyl)silane 348[99]

A mixture of trichlorosilane (**347**, 3.68 mL, 36.4 mmol) and 2-methylallyl chloride (**346**, 3.23 mL, 33.1 mmol) was added dropwise, under argon, into a mixture of triethylamine (4.62 mL, 33.1 mmol), cuprous chloride (0.16 g, 1.66 mmol) and diethyl ether (17 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then at rt for 4 h under argon. The reaction mixture was filtered through Celite® to remove precipitate and the filtrate was concentrated at rt to obtain crude product. Reduced pressure distillation yielded trichloro(2-methylallyl)silane (**348**, 4.24 g, 68%) as a clear colourless liquid.

b.p.: 70 °C (70 mmHg) [lit[99] 136 °C]; δ_H (500 MHz; $CDCl_3$) 4.94 (1H, dq, *J* 3.0, 1.5, 1 of C=CH_2), 4.85-4.84 (1H, m, 1 of C=CH_2), 2.37 (2H, d, *J* 1.0, SiCH_2), 1.88 (3H, dd, *J* 1.4, 0.9, CH_3); δ_C (125 MHz; $CDCl_3$) 136.3 (H_2C=*C*(CH_3)), 114.8 (C=*C*H_2), 34.7 ($SiCH_2$), 24.5 (*C*H_3); *m/z* (EI) 333 (29 %), 284 (45), 219 (25), 146 (30), 69 (100).

Synthesis of (2-Methylallyl)diphenyl(3-phenylprop-2ynyloxy)silane 327h



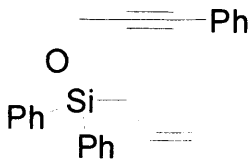
Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 4.2 mL, 4.2 mmol) was added dropwise to a stirred solution of trichloro(2-methylallyl)silane (**348**, 0.40 g, 2.1 mmol) in diethyl ether (1.8 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain (2-methylallyl)diphenylchlorosilane in solution. This solution was cooled to rt and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (**329**, 0.28 g, 2.1 mmol), 4-dimethylaminopyridine (26 mg, 0.21 mmol) and triethylamine (0.29 mL, 2.1 mmol) in dichloromethane (21 mL) under argon at 0 °C. The washings from the flask containing (2-methylallyl)diphenylchlorosilane (dichloromethane, 3 mL) were transferred to the flask containing 3-phenyl-2-propyn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon for 2 days.

The reaction mixture was quenched with sat. aqueous NH_4Cl (15 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 99 : 1) afforded (2-methylallyl)diphenyl(3-phenylprop-2ynyloxy)silane (**327h**, 0.30 g, 39 %) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3071s (=C-H_2), 2914s & 2860m (C-H), 2260w (C≡C), 1639s (C=C), 1589m (C=C aromatic), 1489s (C=C aromatic), 1443s, 1429s, 1375s, 1279s; δ_H (500 MHz; $CDCl_3$) 7.70-7.68 (4H, m, arom.*H*), 7.46-7.29 (11H, m, arom.*H*), 4.67-4.66 (1H, m, 1 of C=CH_2), 4.62-4.61 (1H, m, 1 of C=CH_2), 4.61 (2H, s, OCH_2), 2.29 (2H, d, *J* 1.0, SiCH_2), 1.66 (3H, dd, *J* 1.3, 0.8, CH_3); δ_C (125 MHz; $CDCl_3$) 141.5 (*C*=CH_2), 134.9 (arom.*C*H), 134.0 (arom.C_q), 131.6 (arom.*C*H), 130.0 (arom.*C*H), 128.3 (arom.*C*H), 128.2 (arom.*C*H), 127.8 (arom.*C*H), 122.8 (arom.C_q), 110.9 (C=*C*H_2), 87.3 & 85.5

(*C*≡*C*), 52.8 (O*C*H$_2$), 25.8 (Si*C*H$_2$), 25.4 (*C*H$_3$); *m/z* (FAB pos) 391 (MNa$^+$, 41%), 283 (100), 199 (50), 176 (75); HRMS calculated for $C_{25}H_{24}OSiNa$ (MNa$^+$) 391.1494 Found 391.1498.

Synthesis of (*Z*)-2-Methylbut-2-enyl-diphenyl-3-phenylprop-2-ynyloxysilane 327i



Trichlorosilane (**347**, 0.45 mL, 4.4 mmol), isoprene (**349**, 0.49 mL, 4.9 mmol), bis(benzonitrile)palladium(II) chloride (3.7 mg, 9.8 μM) and triphenylphosphine (5.8 mg, 0.02 mmol) were heated in a sealed tube at 70 °C for 6 h. The reaction mixture was cooled down. ^{1}H NMR spectrum showed it to contain almost exclusively (*Z*)-Trichloro(2-methylbut-2-enyl)silane[100] (**350**).

δ_H (400 MHz; $CDCl_3$) 5.43 (1H, br q, *J* 6.8, C=C*H*), 2.39 (2H, t, *J* 0.7, Si*C*H$_2$), 1.83 (3H, dt, *J* 3.0, 1.5, (*C*H$_3$)C=CH(CH$_3$)), 1.60 (3H, dtq, *J* 6.8, 1.5, 0.7, C=CH(*C*H$_3$)).

Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 8.9 mL, 8.9 mmol) was added dropwise to a solution of (*Z*)-trichloro(2-methylbut-2-enyl)silane (**350**), in the sealed tube, in diethyl ether (3.8 mL) and cooled to –78 °C under argon. The resulting reaction mixture was stirred at –78 °C for 30 minutes followed by stirring at rt overnight. The reaction mixture was diluted with dichloromethane (4mL) and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (**329**, 0.59 g, 4.4 mmol), 4-dimethylaminopyridine (54 mg, 0.44 mmol) and triethylamine (0.62 mL, 4.4 mmol) in dichloromethane (44 mL) under argon at 0 °C. The reaction mixture was stirred at 0 °C for 1 h followed by stirring at rt for 2 days.
The reaction mixture was quenched with sat. aqueous NH_4Cl (30 mL) and extracted with dichloromethane (3 x 80 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Al_2O_3, Petrol 40-60) afforded (*Z*)-2-methylbut-2-enyl-diphenyl-3-phenylprop-2-ynyloxysilane (**327i**, 0.20 g, 12 %) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3069m (C=C-H), 2914m & 2858m (C-H), 2220w (C≡C), 1600m (C=C), 1490s (C=C aromatic), 1428s, 1375s; δ_H (500 MHz; $CDCl_3$) 7.73-7.70 (4H, m, arom.*H*), 7.49-7.30 (11H, m, arom.*H*), 5.14 (1H, br q, *J* 6.7, C=C*H*(CH$_3$)), 4.61 (2H, s,

OC*H*$_2$), 2.25 (2H, br s, SiC*H*$_2$), 1.70 (3H, dt, *J* 2.9, 1.4, (C*H*$_3$)C=CH(CH$_3$)), 1.34 (3H, br d *J* 6.7, C=CH(C*H*$_3$)); δ_C (125 MHz; $CDCl_3$) 134.9 (arom.*C*H), 134.2 (arom.C_q), 131.6 (arom.*C*H), 131.4 (arom.C_q), 130.0 (arom.*C*H), 128.21 (arom.*C*H), 128.16 (arom.*C*H), 127.8 (arom.*C*H), 122.8 ((CH$_3$)*C*=CH(CH$_3$)), 118.2 ((CH$_3$)C=*C*H(CH$_3$)), 87.3 & 85.4 (*C*≡*C*), 52.7 (OCH$_2$), 26.3 ((*C*H$_3$)C=CH(CH$_3$)), 20.8 (SiCH$_2$), 13.8 ((CH$_3$)C=CH(*C*H$_3$)); *m/z* (CI pos) 383 (MH^+, 40%), 330 (100), 313 (54), 216 (75); HRMS calculated for $C_{26}H_{27}OSi$ (MH^+) 383.1831 Found 383.1822.

Synthesis of Crotyltrichlorosilane 352[99]

A mixture of *Z* and *E* crotyl chloride (1 : 6) (**351**, 4.3 mL, 44 mmol) and trichlorosilane (**347**, 6.2 mL, 62 mmol) in diethyl ether (7 mL) was added to a suspension of cuprous chloride (0.14 g, 1.5 mmol) and triethylamine (7.40 mL, 53 mmol) in diethyl ether (22 mL) under argon at 0 °C. Another 20 mL of dry diethyl ether was added to the reaction mixture due to evaporation of solvent, after an exothermic reaction. After stirring at rt for 2 h, the purple precipitate was removed by filtration through Celite® and the filtrate concentrated at rt to obtain the crude product. The crotyltrichlorosilane (**352**, 3.6 g, 43 %) was isolated by reduced pressure distillation as an inseparable mixture of *Z* : *E* diasteroisomers in the ratio of 1 : 6.

b.p.: 70 °C (66 mmHg) [lit[99] 142-144 °C].

(*E*)-Crotyltrichlorosilane

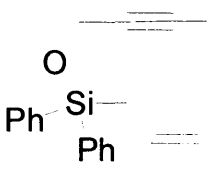
δ_H (500 MHz; $CDCl_3$) 5.61 (1H, dqt, *J* 15.2, 6.5, 1.3, CH$_3$*H*C=C), 5.38 (1H, dtq, *J* 15.2, 7.6, 1.7, HC=C*H*CH$_2$Si), 2.26 (2H, br d, *J* 7.6, SiC*H*$_2$), 1.72 (3H, ddt, *J* 6.5, 1.7, 1.2, C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 130.4 (CH$_3$H*C*=C), 119.2 (HC=*C*HCH$_2$Si), 29.2 (SiCH$_2$), 18.1 (CH$_3$).

(*Z*)-Crotyltrichlorosilane

δ_H (500 MHz; $CDCl_3$) 5.73 (1H, dqt, *J* 13.8, 6.9, 1.4, (CH$_3$)*H*C=C), 5.42 (1H, dtq, *J* 14.5, 6.4, 1.7, HC=C*H*CH$_2$Si), 2.35 (2H, br d, *J* 8.2, SiC*H*$_2$), 1.67 (3H, ddt, *J* 6.9, 1.8, 0.8, C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 128.3 (CH$_3$H*C*=C), 118.6 (HC=*C*HCH$_2$Si), 24.7 (SiCH$_2$), 13.0 (CH$_3$).

m/z (CI pos) 293 (100), 269 (43), 189 (MH^+, 45%), 153 (60) ; HRMS calculated for $C_4H_8SiCl_3$ (MH^+) 188.9461 Found 188.9462.

Synthesis of (*E*)-But-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane 327j

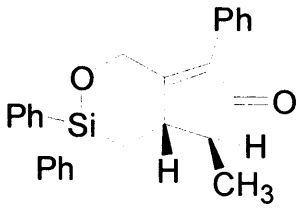


Using the procedure of Garner *et al.*[94,96], a solution of phenylmagnesium bromide (1.0M in THF, 5.3 mL, 5.3 mmol) was added dropwise to a stirred solution of crotyltrichlorosilane (1 : 6 *Z* : *E*) (**352**, 0.50 g, 2.6 mmol) in diethyl ether (2.3 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, warmed to rt and then heated to reflux for 2 h to obtain crotylchlorodiphenylsilane in solution. This solution was cooled to rt and added dropwise to a solution of 3-phenyl-2-propyn-1-ol (**329**, 0.35 g, 2.6 mmol), 4-dimethylaminopyridine (32 mg, 0.26 mmol) and triethylamine (0.37 mL, 2.6 mmol) in dichloromethane (26 mL) under argon at 0 °C. The washings from the flask containing crotylchlorodiphenylsilane (dichloromethane, 4 mL) were transferred to the flask containing 3-phenyl-2-propyn-1-ol and triethylamine and the resulting reaction mixture was stirred at 0 °C for 1 h, followed by stirring at rt under argon for 2 days.

The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Petrol 40-60 / Ether 99.8 : 0.2) afforded (*E*)-but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane (**327j**, 0.28 g, 29 %) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3069s (=C-H), 2916s & 2855s (C-H), 2270w (C≡C), 1610m (C=C), 1589m (C=C aromatic), 1489s (C=C aromatic), 1443m, 1429s, 1371s; δ_H (500 MHz; $CDCl_3$) 7.69-7.67 (4H, m, arom.*H*), 7.46-7.29 (11H, m, arom.*H*), 5.52 (1H, dtq, *J* 15.1, 7.6, 1.5, HC=C*H*CH_2Si), 5.41 (1H, dqt, *J* 15.1, 6.3, 1.3, CH_3*H*C=C), 4.63 (2H, s, OCH_2), 2.21 (2H, br d, *J* 7.6, SiCH_2), 1.61 (3H, ddt, *J* 6.3, 1.4, 1.3, CH_3); δ_C (125 MHz; $CDCl_3$) 134.9 (arom.*C*H), 134.2 (arom.C_q), 131.6 (arom.*C*H), 129.0 (arom.*C*H), 128.24 (arom.*C*H), 128.17 (arom.*C*H), 127.8 (arom.*C*H), 125.9 & 124.4 (*C*=*C*), 122.8 (arom.C_q), 87.3 & 85.4 (*C*≡*C*), 52.8 (OCH_2), 20.0 ($SiCH_2$), 18.1 (CH_3); *m/z* (CI pos) 369 (MH^+, 9%), 313 (100), 283 (100), 199 (45); HRMS calculated for $C_{25}H_{25}OSi$ (MH^+) 369.1675 Found 369.1664.

Synthesis of exo-9-Methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one 328j



Using the procedure of Sugihara *et al.*[29], a solution of (*E*)-but-2-enyldiphenyl(3-phenylprop-2-ynyloxy)silane (**327j**, 0.12 g, 0.33 mmol) in 1,2-dichloroethane (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.16 g, 0.47 mmol) in 1,2-dichloroethane (1.5 mL) under argon at rt. The reaction mixture was stirred at rt for 1 h. *n*-Butyl methyl sulfide (0.14 mL, 1.1 mmol) was added and the reaction mixture was heated to reflux under argon for 2 days.

The reaction mixture was cooled, concentrated *in vacuo* and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / Ether 7 : 3) to afford exo-9-methyl-3,3,7-triphenyl-4-oxa-3-silabicyclo[4.3.0]non-6-en-8-one (328j, 43 mg, 33%) as a pale yellow oil.

ν_{max} (neat)/cm^{-1} 2926m & 2852m (C-H), 1705br s (C=O & C=C), 1589m (C=C aromatic), 1495m (C=C aromatic), 1445m, 1429s; δ_H (500 MHz; $CDCl_3$) 7.75-7.73 (2H, m, arom.*H*), 7.58-7.56 (2H, m, arom.*H*), 7.52-7.47 (2H, m, arom.*H*), 7.44-7.33 (7H, m, arom.*H*), 7.28-7.26 (2H, m, arom.*H*), 5.19 (1H, d, *J* 16.6, 1 of OCH_2), 5.00 (1H, dd, *J* 16.5, 1.3, 1 of OCH_2), 2.90-2.84 (1H, m, $SiCH_2CH$), 2.29 (1H, qd, *J* 7.3, 2.5, $OCCH(CH_3)$), 1.97 (1H, dd, *J* 14.6, 5.0, 1 of $SiCH_2$), 1.30 (3H, d, *J* 7.4, CH_3), 1.26 (1H, dd, *J* 14.3, 13.5, 1 of $SiCH_2$); δ_C (125 MHz; $CDCl_3$) 207.8 (C=O), 169.9 (*C*=CPh), 137.2 (OCH_2C=*C*Ph), 134.3 (arom.*C*H), 134.2 (arom.*C*H), 134.0 (arom.C_q), 133.5 (arom.C_q), 130.7 (arom.C_q), 130.54 (arom.*C*H), 130.53 (arom.*C*H), 129.0 (arom.*C*H), 128.34 (arom.*C*H), 128.30 (arom.*C*H), 128.11 (arom.*C*H), 128.08 (arom.*C*H), 63.1 (OCH_2), 51.7 ($OCCH(CH_3)$), 44.3 ($SiCH_2CH$), 17.5 ($SiCH_2$), 14.6 (CH_3); *m/z* (CI pos) 397 (MH^+, 100%), 319 (55), 199 (15); HRMS calculated for $C_{26}H_{25}O_2Si$ (MH^+) 397.1624 Found 397.1631

4.2.3 Synthesis of silyl enol ethers

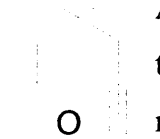
Synthesis of isophorone oxide 356a[102]

In a 3-necked flask, equipped with a thermometer, was placed a solution of isophorone (**355a**, 1.0 g, 7.2 mmol) and 30% aqueous hydrogen peroxide (2.5 mL, 22 mmol), in methanol (8 mL). After the contents of the flask had been cooled to 15 °C, 6M sodium hydroxide (0.6 mL, 3.6 mmol) was added dropwise, with stirring. During the addition, the temperature of the reaction was maintained at 20-25 °C. The resulting reaction mixture was stirred at 20-25 °C for 105 minutes.

The reaction mixture was then poured into H_2O (30 mL). The resulting mixture was extracted with diethyl ether (4 x 25 mL) and the combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane / EtOAc 9 : 1) afforded isophorone oxide (**356a**, 0.77 g, 69%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 2872s (C-H), 1717s (C=O), 1448m, 1398s, 1309m; δ_H (500 MHz; $CDCl_3$) 2.99 (1H, br s, O=CC*H*), 2.56 (1H, dd, *J* 13.3, 0.7, 1 of O=CCH_2), 2.02 (1H, br d, *J* 15.0, 1 of CH_2), 1.75 (1H, ddd, *J* 13.4, 3.1, 1.0, 1 of O=CCH_2), 1.64 (1H, dd, *J* 14.9, 2.1, 1 of CH_2), 1.37 (3H, s, OCCH_3), 0.97 (3H, s, CH_3), 0.86 (3H, s, CH_3); δ_C (125 MHz; $CDCl_3$) 207.8 (*C*=O), 64.2 (O*C*CH_3), 61.3 (O*C*H), 47.9 (O=*C*CH_2), 42.7 (*C*H_2), 36.0 (*C*$(CH_3)_2$), 30.7 (*C*H_3), 27.8 (*C*H_3), 23.9 (OC*C*H_3); *m/z* (CI pos) 155 (MH^+, 71%), 141 (75), 109 (100); HRMS calculated for $C_9H_{15}O_2$ (MH^+) 155.1072 Found 155.1072.

Synthesis of 4,4-dimethyl-6-heptyn-2-one 357a[101]



A solution of isophorone oxide (**356a**, 5.0 g, 32 mmol) and (*p*-toluenesulfonyl)hydrazine (6.0 g, 32 mmol) in ethanol (260 mL) under nitrogen, were stirred at rt for 2 h. A light yellow precipitate was formed. The reaction mixture was heated to 55 °C under nitrogen overnight.

The clear orange solution was cooled to rt, diluted with H_2O (65 mL), and extracted with chloroform (4 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane

/ EtOAc 9 : 1) afforded 4,4-dimethyl-6-heptyn-2-one (**357a**, 1.3 g, 29%) as a colourless oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3296s (C≡C-H), 2878s (C-H), 2116w (C≡C), 1713s (C=O), 1366s, 1159m, 1049m; δ_H (500 MHz; $CDCl_3$) 2.46 (2H, s, OCCH_2), 2.24 (2H, d, *J* 2.7, HC≡CCH_2), 2.11 (3H, s, OCCH_3), 1.98 (1H, t, *J* 2.7, *H*C≡C), 1.06 (6H, s, 2 x CH_3); δ_C (125 MHz; $CDCl_3$) 208.2 (*C*=O), 82.1 (*C*≡C-H), 70.3 (C≡*C*-H), 52.2 (OC*C*H_2), 33.2 (*C*$(CH_3)_2$), 32.0 (OC*C*H_3), 31.2 (H_2*C*C≡C-H), 27.0 (2 x *C*H_3).

Synthesis of 2,3,5,5-tetramethylcyclohex-2-en-1-one 355b[103]

To a solution of sodium ethoxide, prepared by reacting sodium (0.46 g, 20 mmol) with ethanol (9.4 mL), was added over 20 minutes a solution of mesityl oxide (**353**, 2.0 g, 20 mmol) and methyl-3-oxopentanoate (**354**, 2.7g, 21 mmol) in ethanol (11.7 mL). The reaction mixture was heated to 80 °C under nitrogen, overnight.

The reaction mixture was poured into cold 25% aqueous HCl, extracted with 50% diethyl ether in hexane (4 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled under reduced pressure to obtain 2,3,5,5-tetramethylcyclohex-2-en-1-one (**355b**, 1.1 g, 34%) as a clear oil.

b.p.: 62-66 °C (2 mmHg) [lit[103] 71-74 °C (1 mmHg)]; ν_{max} (neat)/cm^{-1} 2957s & 2868s (C-H), 1667s & 1639s (C=O & C=C); δ_H (300 MHz; $CDCl_3$) 2.24 (2H, s, OCCH_2), 2.21 (2H, s, CH_2), 1.90 (3H, s, OCC(CH_3)=C(CH_3)), 1.77 (3H, s, OCC(CH_3)=C(CH_3)), 1.00 (6H, s, 2 x CH_3); δ_C (75 MHz; $CDCl_3$) 199.3 (*C*=O), 152.3 & 130.1 (*C*=*C*), 51.1 (OCCH_2), 47.0 (*C*H_2), 32.7 (*C*$(CH_3)_2$), 28.3 (2 x *C*H_3), 21.6 & 10.5 (*C*H_3C=C*C*H_3); *m/z* (EI pos) 152 (M^+, 70%), 131 (39), 96 (100); HRMS calculated for $C_{10}H_{16}O$ (M^+) 152.1201 Found 152.1202.

Synthesis of 2,3-Epoxy-2,3,5,5-tetramethylcyclohexanone 356b

Using the procedure of House *et al.*[102], in a 2-necked flask, equipped with a thermometer, was placed a solution of 2,3,5,5-tetramethylcyclohex-2-en-1-one (**355b**, 2.25 g, 14.8 mmol) and 30% aqueous hydrogen peroxide (5.0 mL, 44 mmol), in methanol (17.3 mL). After the

contents of the flask had been cooled to 15 °C, 6M sodium hydroxide (1.2 mL, 7.4 mmol) was added dropwise, with stirring. During the addition, the temperature of the reaction was maintained at 20-25 °C. The resulting reaction mixture was stirred at rt, overnight.

The reaction mixture was then poured into H_2O (30 mL). The resulting mixture was extracted with diethyl ether (4 x 50 mL) and the combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane / EtOAc 95 : 5) afforded 2,3-epoxy-2,3,5,5-tetramethylcyclohexanone (**356b**, 1.77 g, 71%) as a colourless oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2932s (C-H), 1713s (C=O), 1369m, 1348m, 1105m; δ_H (500 MHz; $CDCl_3$) 2.74 (1H, d, *J* 13.2, 1 of O=CCH_2), 2.10 (1H, d, *J* 14.9, 1 of CH_2), 1.84 (1H, dd, *J* 13.2, 2.3, 1 of O=CCH_2), 1.68 (1H, dd, *J* 15.0, 2.2, 1 of CH_2), 1.41 (3H, s, OCCH_3), 1.40 (3H, s, OCCH_3), 0.99 (3H, s, CH_3), 0.86 (3H, s, CH_3); δ_C (125 MHz; $CDCl_3$) 208.7 (*C*=O), 67.6 (O=*C*CCH_3), 64.0 (O*C*CH_3), 48.2 (O=C*C*H_2), 44.4 (*C*H_2), 35.0 (*C*$(CH_3)_2$), 30.9 (*C*H_3), 27.9 (*C*H_3), 21.6 (OC*C*H_3), 11.2 (OC*C*H_3); *m/z* (EI pos) 168 (M^+, 26%), 153 (60), 111 (42), 97 (46), 85 (65), 71 (75), 57 (100); HRMS calculated for $C_{10}H_{16}O_2$ (M^+) 168.1150 Found 168.1149.

Synthesis of 4,4-Dimethyloct-6-yn-2-one 357b

Using the procedure of Wei *et al.*[101], a solution of 2,3-epoxy-2,3,5,5-tetramethylcyclohexanone (**356b**, 0.30 g, 1.8 mmol) and (*p*-toluenesulfonyl)hydrazine (0.33 g, 1.8 mmol) in ethanol (16 mL) under nitrogen, were stirred at rt for 2 h. The reaction mixture was heated to 55 °C under nitrogen, for 2 h.

The clear orange solution was cooled to rt, diluted with H_2O (50 mL), and extracted with chloroform (3 x 50 mL). The combined organic extracts were washed with H_2O (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane / EtOAc 9 : 1) afforded 4,4-dimethyloct-6-yn-2-one (**357b**, 0.13 g, 48%) as a colourless oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2874s (C-H), 1715s (C=O), 1364m, 1157m; δ_H (300 MHz; $CDCl_3$) 2.42 (2H, s, OCCH_2), 2.16 (2H, q, *J* 2.5, CH_2C≡CCH_3), 2.14 (3H, s, OCCH_3),

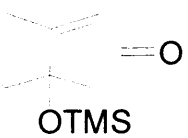
1.79 (3H, t, *J* 2.5, H_3CC≡C), 1.05 (6H, s, 2 x CH_3); δ_C (75 MHz; $CDCl_3$) 208.6 (*C*=O), 77.6 & 76.7 (*C*≡*C*), 52.7 (OCCH_2), 33.7 (*C*$(CH_3)_2$), 32.2 (OCCH_3), 32.1 (H_2*C*C≡CCH_3), 27.0 (2 x *C*H_3), 3.4 (C≡C*C*H_3); *m/z* (EI pos) 175 (81%), 151 (M-H^+, 26), 137 (20), 123 (55), 109 (95), 91 (100).

Synthesis of 4,4-Dimethyl-2-trimethylsilyloxyoct-1-en-6-yne 272b

n-Butyllihium (1.6 M in hexane, 0.34 mL, 0.54 mmol) was added dropwise to a solution of diisopropylamine (80 μL, 0.57 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to –78 °C and a solution of 4,4-dimethyloct-6-yn-2-one (**357b**, 80 mg, 0.52 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, followed by addition of chlorotrimethylsilane (72 μL, 0.57 mmol). The reaction mixture was warmed to rt over 1 h, quenched with sat aqueous sodium hydrogen carbonate (2 mL) and extracted with diethyl ether (3 x 20 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane / EtOAc 99 : 1) afforded 4,4-dimethyl-2-trimethylsilyloxyoct-1-en-6-yne (**272b**, 12 mg, 10%) as a pale yellow oil.

ν_{max} (neat)/cm^{-1} 2961s (C=CH_2), 2924s & 2856m (C-H), 1634m (C=C), 1469m, 1261s; δ_H (300 MHz; $CDCl_3$) 4.10 (1H, s, 1 of C=CH_2), 4.07 (1H, s, 1 of C=CH_2), 2.08 (2H, q, *J* 2.5, CH_2C≡CCH_3), 2.01 (2H, s, CH_2C=CH_2), 1.80 (3H, t, *J* 2.5, H_3CC≡C), 0.98 (6H, s, 2 x CH_3), 0.21 (9H, s, OSi(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 157.8 (*C*=CH_2), 92.4 (C=*C*H_2), 77.6 & 77.8 (*C*≡*C*), 47.7 (*C*H_2C=CH_2), 33.7 (*C*$(CH_3)_2$), 32.3 (H_2*C*C≡CCH_3), 27.1 (2 x *C*H_3), 3.4 (C≡C*C*H_3), 0.04 (OSi(*C*H_3)$_3$).

Synthesis of 2,7,7-Trimethyl-5-trimethylsilanyloxybicyclo[3.3.0]oct-1-en-3-one 358

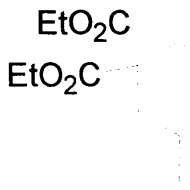


Using the procedure of Mukai *et al.*[91], a solution of 4,4-dimethyl-2-trimethylsilyloxyoct-1-en-6-yne (**272b**, 12 mg, 75 μmol) in acetonitrile (0.5 mL) was added to a stirred solution of dicobalt octacarbonyl (0.03 g, 91 μmol) in acetonitrile (0.5 mL), at rt under nitrogen and the mixture was stirred for 1 h. The resulting reaction mixture was heated to 75 °C overnight.

The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (Florisil®, Petrol 30-40 / Ether 99: 1 to 80 : 20) to obtain 2,7,7-trimethyl-5-trimethylsilanyloxybicyclo[3.3.0]oct-1-en-3-one (**358**, 3 mg, 19%) as a yellow oil.

δ_H (500 MHz; $CDCl_3$) 2.59 (1H, d, *J* 18.1, 1 of OCCH_2), 2.55 (1H, d, *J* 16.4, 1 of CH_2C=C), 2.40 (1H, d, *J* 18.0, 1 of OCCH_2), 2.35 (1H, d, *J* 16.4, 1 of CH_2C=C), 2.09 (1H, d, *J* 13.7, 1 of CH_2COSi(CH_3)$_3$), 1.70 (3H, d, *J* 1.6, C=CCH_3), 1.38 (1H, d, *J* 13.7, 1 of CH_2COSi(CH_3)$_3$), 1.34 (3H, s, CH_3), 1.01 (3H, s, CH_3), 0.08 (9H, s, OSi(CH_3)$_3$).

Synthesis of Diethyl hept-6-yn-2-one-4,4-dicarboxylate 361a



Using the procedure of Trost *et al.*[90], a solution of diethyl propargylmalonate (**276a**, 1.10 g, 5.55 mmol), chloroacetone (**360**, 1.33 mL, 16.6 mmol), potassium carbonate (2.3 g, 17 mmol) and sodium iodide (83 mg, 0.56 mmol), in acetone (22 mL) was heated to reflux, under nitrogen, overnight.

The reaction mixture was filtered, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Hexane / EtOAc 7 : 3) to obtain diethylhept-6-yn-2-one-4,4-dicarboxylate (**361a**, 0.95 g, 67%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3281s (C≡C-H), 2984s & 2939m (C-H), 2120w (C≡C), 1722br (C=O ester and ketone), 1467m, 1367s, 1286s; δ_H (300 MHz; $CDCl_3$) 4.22 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 4.13 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.33 (2H, s, O=CCH_2), 3.00 (2H, d *J* 2.7, H_2CC≡CH), 2.17 (3H, s, O=CCH_3), 2.00 (1H, t, *J* 2.7, C≡C*H*), 1.23 (6H, t, *J* 7.2, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 205.3 (*C*=O ketone), 169.0 (*C*=O ester), 79.3 (*C*≡CH), 71.5 (C≡*C*H), 61.9 (OCH_2), 54.3 (O_2CCCO_2), 45.1 (O=CCH_2), 30.1 (O=CCH_3), 23.1 (H_2CC≡CH), 13.9 (OCH_2CH_3); *m/z* (CI pos) 255 (MH^+, 84%), 181 (100); HRMS calculated for $C_{13}H_{19}O_5$ (MH^+) 255.1232 Found 255.1234.

Synthesis of 1-Bromo-3-phenylprop-2-yne 359[104]

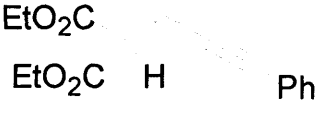
To a mixture of 3-phenylprop-2yn-1-ol (**329**, 0.50 g, 3.8 mmol) and pyridine (40 μL, 0.5 mmol) in diethyl ether (0.6 mL), under nitrogen

at 0 °C, was added phosphorus tribromide (0.47 mL, 4.9 mmol) dropwise. The resulting reaction mixture was heated to 50 °C for 2.5 h.

The reaction mixture was cooled and poured into ice.H_2O (30 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (4 x 50 mL). The combined organic extracts were successively washed with sat. aqueous $NaHCO_3$ (2 x 100 mL), H_2O (2 x 100 mL) and brine (2 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane) afforded 1-bromo-3-phenylprop-2-yne (**359**, 0.6 g, 82%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 3057m (C-H), 2219s (C≡C), 1597m (C=C aromatic), 1490s (C=C aromatic), 1441s, 1271sm 1204s; δ_H (300 MHz; $CDCl_3$) 7.47-7.44 (2H, m, arom.*H*), 7.35-7.31 (3H, m, arom.*H*), 4.17 (2H, s, C*H*$_2$); δ_C (75 MHz; $CDCl_3$) 131.8 (arom.*C*H), 128.8 (arom.*C*H), 128.3 (arom.*C*H), 122.1 (arom.*C*$_q$), 86.7 & 84.2 (*C*≡*C*), 15.2 (*C*H$_2$); *m/z* (CI pos) 197 &195 (MH^+, 36% & 38%), 133 (19), 115 (60), 105 (100).

Synthesis of Diethyl 2-(3-phenylprop-2-ynyl)malonate 276b



Using the procedure of Marvel and Hager.[89], diethyl malonate (**274**, 4.1 g, 26 mmol) was added through a dropping funnel to a solution of sodium ethoxide prepared by the addition of sodium (0.59 g, 26 mmol), in small pieces, to ethanol (15 mL) under nitrogen. To this reaction mixture at 50 °C was added 1-bromo-3-phenylprop-2-yne (**359**, 5.0 g, 26 mmol) dropwise. The reaction mixture was heated to reflux, overnight.

Ethanol was removed *in vacuo* and the residue was dissolved in H_2O (20 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (5 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Toluene / EtOAc 99 : 1) afforded diethyl 2-(3-phenylprop-2-ynyl)malonate (**276b**, 3.0 g, 43%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 2982s, 2938m & 2907m (C-H), 1733s (C=O), 1598m (C=C aromatic), 1491s (C=C aromatic), 1465m, 1443s, 1369s; δ_H (300 MHz; $CDCl_3$) 7.38-7.35 (2H, m, arom.*H*), 7.28-7.27 (3H, m, arom.*H*), 4.25 (4H, q, *J* 7.2, OC*H*$_2$), 3.65 (1H, t, *J* 7.7, O_2CCHCO_2), 3.00 (2H, d, *J* 7.7, *H*$_2$CC≡CPh), 1.29 (6H, t, *J* 7.2, OCH_2CH_3); δ_C (75

MHz; $CDCl_3$) 168.1 (*C*=O), 131.6 (arom.*C*H), 128.2 (arom.*C*H), 127.9 (arom.*C*H), 123.2 (arom.C_q), 85.4 & 82.4 (*C*≡*C*), 61.7 (OCH_2), 51.5 (O_2CCHCO_2), 19.4 ($H_2CC{\equiv}CPh$), 14.1 (OCH_2CH_3); *m/z* (CI pos) 275 (MH^+, 90%), 229 (45), 201 (95), 161 (100); HRMS calculated for $C_{16}H_{19}O_4$ (MH^+) 275.1283 Found 275.1284.

A side product of the reaction, diethyl 2,2-di-(3-phenylprop-2-ynyl)malonate (**277b**, 2.2 g, 22%) was isolated as a white crystalline solid.

m.p.: 81-82 °C; Found C 76.9, H 6.2; $C_{25}H_{24}O_4$ requires C 77.3, H 6.2% ; ν_{max} ($CHCl_3$ cast)/cm^{-1} 2981s & 2936m (C-H), 1732 (C=O), 1598m (C=C aromatic), 1491s (C=C aromatic), 1465m, 1443s, 1367m, 1325s, 1297s; δ_H (300 MHz; $CDCl_3$) 7.40-7.37 (4H, m, arom.*H*), 7.29-7.27 (6H, m, arom.*H*), 4.27 (4H, q, *J* 7.2, OCH_2), 3.26 (4H, s, $H_2CC{\equiv}CPh$), 1.29 (6H, t, *J* 7.2, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 168.9 (*C*=O), 131.7 (arom.*C*H), 128.2 (arom.*C*H), 128.0 (arom.*C*H), 123.2 (arom.C_q), 84.1 & 83.7 (*C*≡*C*), 62.0 (OCH_2), 57.1 (O_2CCCO_2), 23.7 ($H_2CC{\equiv}CPh$), 14.1 (OCH_2CH_3); *m/z* (CI pos) 389 (MH^+, 12%), 242 (60), 193 (65), 165 (100), 115 (45), 91 (54).

Synthesis of Diethyl 7-phenylhept-6-yn-2-one-4,4-dicarboxylate 361b

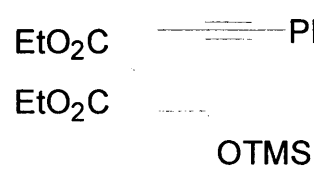
Using the procedure of Trost *et al.*[90], a solution of diethyl 2-(3-phenylprop-2-ynyl)malonate (**276b**, 1.8 g, 6.6 mmol), chloroacetone (**360**, 1.6 mL, 20 mmol), potassium carbonate (2.7 g, 20 mmol) and sodium iodide (0.10 g, 0.7 mmol), in acetone (36 mL) was heated to reflux, under nitrogen, overnight.

The reaction mixture was filtered, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Toluene / EtOAc 24 : 1) followed by chromatotron (SiO_2, Toluene / EtOAc 99 : 1) to obtain diethyl 7-phenylhept-6-yn-2-one-4,4-dicarboxylate (**361b**, 0.9 g, 41%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 2982s & 2936s (C-H), 1722br (C=O ester & ketone), 1590m (C=C aromatic), 1491s (C=C aromatic), 1443s, 1391m, 1367s, 1286s; δ_H (300 MHz; $CDCl_3$) 7.34-7.32 (2H, m, arom.*H*), 7.28-7.26 (3H, m, arom.*H*), 4.21 (2H, dq, *J* 10.8, 7.2, 2 of

OC*H*$_2$), 4.20 (2H, dq, *J* 10.8, 7.1, 2 of OC*H*$_2$), 3.38 (2H, s, O=CC*H*$_2$), 3.20 (2H, s, *H*$_2$CC≡CPh), 2.18 (3H, s, O=CC*H*$_3$), 1.24 (6H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 205.4 (*C*=O ketone), 169.2 (*C*=O ester), 135.6 (arom.*C*H), 128.2 (arom.*C*H), 128.0 (arom.*C*H), 123.1 (arom.*C*$_q$), 84.7 & 83.7 (*C*≡*C*), 62.0 (O*C*H$_2$), 54.8 (O$_2$C*C*CO$_2$), 45.5 (O=C*C*H$_2$), 30.3 (O=C*C*H$_3$), 24.2 (H$_2$*C*C≡CPh), 14.0 (OCH$_2$*C*H$_3$); *m/z* (CI pos) 331 (MH^+, 100%), 257 (96), 215 (50), 161 (75), 105 (90); HRMS calculated for $C_{19}H_{23}O_5$ (MH^+) 331.1545 Found 331.1547.

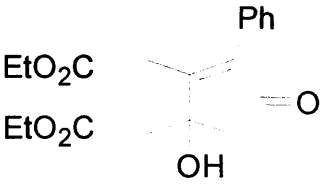
Synthesis of Diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate 362c



n-Butyllithium (1.6 M in hexane, 0.23 mL, 0.36 mmol) was added dropwise to a solution of diisopropylamine (51 µL, 0.36 mmol) in THF (2 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to –78 °C, a solution of 4,4-diethyl-7-phenylhex-6-yne -2-onemalonate (**361b**, 0.10 g, 0.30 mmol) in THF (1 mL) was added dropwise and stirred for 40 minutes. Chlorotrimethylsilane (46 µL, 0.36 mmol) was added dropwise and the reaction mixture stirred for 10 minutes. The reaction mixture was warmed to rt over 1 h, quenched with sat. aqueous sodium hydrogen carbonate (3 mL) and extracted with diethyl ether (3 x 10 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (**362c**, 0.15 g) as a yellow oil, slightly contaminated with silyl impurities.

δ_H (300 MHz; C_6D_6) 7.45-7.41 (2H, m, arom.*H*), 6.99-6.94 (3H, m, arom.*H*), 4.38 (1H, s, 1 of C=C*H*$_2$), 4.19 (1H, s, 1 of C=C*H*$_2$), 4.14 (2H, dq, *J* 10.8, 7.1, 2 of OC*H*$_2$), 3.96 (2H, dq, *J* 10.8, 7.1, 2 of OC*H*$_2$), 3.52 (2H, s, C*H*$_2$C=C), 3.37 (2H, s, *H*$_2$CC≡CPh), 0.96 (6H, t, *J* 7.2, OCH$_2$C*H*$_3$), 0.17 (9H, s, Si(C*H*$_3$)$_3$); δ_C (75 MHz; C_6D_6) 169.9 (*C*=O), 155.3 (*C*=CH$_2$), 132.0 (arom.*C*H), 128.5 (arom.*C*H), 128.3 (arom.*C*H), 124.1 (arom.*C*$_q$), 93.5 (C=*C*H$_2$), 85.9 & 84.1 (*C*≡*C*), 61.4 (O*C*H$_2$), 56.5 (O$_2$C*C*CO$_2$), 39.8 (*C*H$_2$C=CH$_2$), 24.0 (H$_2$*C*C≡CPh), 14.1 (OCH$_2$*C*H$_3$), -0.2 Si(*C*H$_3$)$_3$).

Synthesis of Diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate 364



Method 1

Using the procedure of Mukai *et al.*[91], a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (**362c**, 0.11 g, 0.27 mmol) in acetonitrile (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.11 g, 0.35 mmol) in acetonitrile (1 mL), at rt under nitrogen, and stirred for 1 h. The resulting reaction mixture was heated to 75 °C overnight.

The reaction mixture was cooled and a solution of *para*-toluenesulfonic acid monohydrate (0.10 g, 0.6 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 40 min. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / EtOAc 4 : 1) to obtain diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (**364**, 25 mg, 23%) as a thick oil which could be recrystallised from ether / hexane mixture to obtain a white crystalline solid.

Method 2

To a solution of dicobalt octacarbonyl (0.11 g, 0.33 mmol) in toluene (1 mL), at rt under nitrogen, was added a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (**362c**, 0.10 g, 0.25 mmol) in toluene (1 mL) and stirred for 1 h. The resulting reaction mixture was heated to reflux for 4.5 h.

The reaction mixture was cooled and a solution of *para*-toluenesulfonic acid monohydrate (0.10 g, 0.5 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Petrol 40-60 / EtOAc 7 : 3) to obtain diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (**364**, 31 mg, 29%) as a thick oil which could be recrystallised from ether / hexane mixture to obtain a white crystalline solid.

Method 3

Using the procedure of Sugihara *et al.*[29], a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (**362c**, 0.13 g, 0.33 mmol) in 1,2-dichloroethane (1.9 mL) was added to a solution of dicobalt octacarbonyl (0.21 g, 0.62 mmol) in 1,2-dichloroethane (1.4 mL) under argon at rt. The reaction mixture was stirred at rt for 1.5 h. *n*-Butyl methyl sulphide (0.14 mL, 1.2 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled and a solution of *para*-toluenesulfonic acid monohydrate (0.13 g, 0.53 mmol) in methanol (3 mL) was added and the mixture was stirred at rt for 3 h.

The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, Hexane / EtOAc 7 : 3) to obtain diethyl 5-hydroxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (**364**, 25 mg, 24%) as a thick oil which could be recrystallised from ether / hexane mixture to obtain a white crystalline solid.

m.p.: 112-113 °C; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3419 br s (O-H), 2928s (C-H), 1717s & 1699s (C=O), 1500m (C=C aromatic), 1447m (C=C aromatic), 1367m, 1256s, 1184s; δ_H (500 MHz; C_6D_6) 7.73-7.71 (2H, m, arom.*H*), 7.19-7.17 (2H, m, arom.*H*), 7.11-6.99 (1H, m, arom.*H*), 4.13 (1H, d, *J* 19.0, 1 of CH_2C=CPh), 4.03 (2H, q, *J* 7.1, 2 of OCH_2), 3.85 (1H, dq, *J* 10.8, 7.1, 1 of OCH_2), 3.72 (1H, dq, *J* 10.8, 7.1, 1 of OCH_2), 3.19 (1H, d, *J* 19.0, 1 of CH_2C=CPh), 2.94 (1H, d, *J* 13.9, 1 of CCH_2C(OH)), 2.49 (1H, d, *J* 17.7, 1 of OCCH_2), 2.22 (1H, d, *J* 17.7, 1 of OCCH_2), 2.13 (1H, d, *J* 13.9, 1 of CCH_2C(OH)), 0.95 (3H, t, *J* 7.1, OCH_2CH_3), 0.78 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (125 MHz; C_6D_6) 205.1 (*C*=O ketone), 174.8 (*C*=CPh), 171.9 (*C*=O ester), 170.9 (*C*=O ester), 135.1 (C=*C*Ph), 131.1 (arom.C_q), 129.2 (arom.*C*H), 128.8 (arom.*C*H), 128.7 (arom.*C*H), 81.8 (*C*(OH)), 62.2 (O*C*H_2), 61.8 (O*C*H_2), 61.7 (O_2CCCO_2), 49.0 (OC*C*H_2), 44.5 (C*C*H_2C(OH)), 35.0 (*C*H_2C=CPh), 13.9 (OCH_2CH_3), 13.8 (OCH_2CH_3); *m/z* (FAB pos) 359 (MH^+, 3%), 338 (25), 307 (26), 289 (12), 154 (100); HRMS calculated for $C_{20}H_{23}O_6$ (MH^+) 359.1495 Found 359.1502.

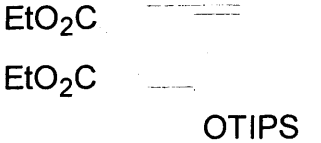
Synthesis of Ethyl 2-(2-oxopropyl)-5-phenylpent-4-ynoate 365

Using the procedure of Krafft *et al.*[35], a solution of diethyl-7-phenyl-2-trimethylsilyloxyhept-1-en-6yne-4,4-dicarboxylate (**362c**, 0.13 g, 0.32 mmol) in dichloromethane (1.5 mL) was added to a solution of dicobalt octacarbonyl (0.16 g, 0.47 mmol) in dichloromethane (1 mL) under nitrogen at rt. The reaction mixture was stirred at rt for 1 h and then concentrated *in vacuo* to obtain a red residue (0.32 g).

A solution of the above residue in H_2O (9.4 mL) and cetyltrimethylammoniun bromide (0.10 g, 0.28 mmol) was heated to 70 °C for 2 days. The reaction mixture was cooled to rt, filtered and extracted with diethyl ether (5 x 25 mL). The combined ethereal extracts were successively washed with 2M aqueous HCl (2 x 100 mL) and H_2O (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Toluene / EtOAc 97 : 3) afforded ethyl 2-(2-oxopropyl)-5-phenylpent-4-ynoate (**365**, 5 mg, 7%) as a yellow oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2908s & 2856s (C-H), 1717s (C=O), 1599w & 1490s (C=C aromatic), 1443s, 1367s, 1181s; δ_H (500 MHz; C_6D_6) 7.45-7.43 (2H, m, arom.*H*), 6.99-6.96 (3H, m, arom.*H*), 4.00-3.95 (2H, m, OCH_2), 3.16-3.11 (1H, m CO_2CH), 2.83 (1H, dd, *J* 18.0, 8.4, 1 of CH_2CO), 2.67 (1H, dd, *J* 17.0, 7.1, 1 of $CH_2C{\equiv}CPh$), 2.60 (1H, dd, *J* 17.0, 7.1, 1 of $CH_2C{\equiv}CPh$), 2.31 (1H, dd, *J* 18.0, 8.4, 1 of CH_2CO), 1.65 (3H, s, CH_3CO), 0.96 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (75 MHz; C_6D_6) 204.6 (*C*=O ketone), 173.1 (*C*=O ester), 131.9 (arom.*C*H), 128.5 (arom.*C*H), 128.1 (arom.*C*H), 124.0 (arom.C_q), 86.9 & 83.3 ($C{\equiv}C$), 60.7 (OCH_2), 43.6 ($OCCH_2$), 39.6 (C*H*), 29.3 ($OCCH_3$), 22.1 ($H_2CC{\equiv}CPh$), 14.1 (OCH_2CH_3); *m/z* (FAB pos) 281 (MNa^+, 100%), 276 (7); HRMS calculated for $C_{16}H_{18}O_3Na$ (MNa^+) 281.1148 Found 281.1151.

Synthesis of Diethyl 2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate 367a



n-Butyllithium (1.6 M in hexane, 0.30 mL, 0.47 mmol) was added dropwise to a solution of diisopropylamine (70 μL, 0.47 mmol) in THF (2.5 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to –78 °C, a solution of diethylhept-6-yn-2-one-4,4-dicarboxylate (**361a**, 0.10 g, 0.39 mmol) in THF (1.5 mL) was added dropwise and stirred for 1.5 h. Triisopropylsilyl triflate (0.13 mL, 0.47 mmol) was added dropwise

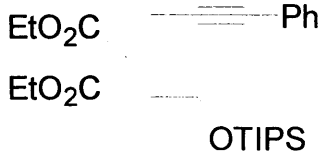
and the reaction mixture was stirred at –78 °C for 1 h. The reaction mixture was warmed to rt over 1 h, quenched with sat. aqueous sodium hydrogen carbonate (3 mL) and extracted with diethyl ether (3 x 10 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane / EtOAc / Et_3N 96 : 3 : 1) afforded diethyl 2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (**367a**, 18 mg, 11%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 3270s (C≡C-H), 2943s & 2867s (C-H), 1739s (C=O), 1634m, 1467m; δ_H (400 MHz; C_6D_6) 4.30 (1H, d, *J* 0.9, 1 of C=CH_2), 4.19 (1H, d, *J* 0.8, 1 of C=CH_2), 4.07 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.97 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.35 (2H, d *J* 2.7, CH_2C≡C), 3.29 (2H, s, CH_2C=C), 1.74 (1H, t, *J* 2.7, C≡C-*H*), 1.14-1.10 (21H, m, SiC*H*(CH_3)$_2$), 0.94 (6H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; C_6D_6) 169.6 (*C*=O), 155.8 ($SiOC=CH_2$), 93.3 (C=*C*H_2), 80.0 (*C*≡CH), 71.8 (C≡*C*H), 61.5 (OCH_2), 56.7 (O_2CCCO_2), 39.4 (*C*H_2C=C), 23.3 (H_2CC≡CH), 18.2 (SiCH(*C*H_3)$_2$), 13.9 (Si*C*H), 13.1 (OCH_2CH_3); *m/z* (FAB pos) 411 (MH^+, 100%), 367 (90), 157 (30); HRMS calculated for $C_{22}H_{39}O_5Si$ (MH^+) 411.2567 Found 411.2570.

Diethyl 7-trisopropylsilyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (**367b**, 40 mg, 18%) was also isolated from the crude mixture as a yellow oil.

ν_{max} (neat)/cm^{-1} 2944s (=C-H_2), 2893m & 2867s (C-H), 2180w (C≡C), 1742s (C=O), 1660w (C=C), 1464m, 1290m, 1203s; δ_H (300 MHz; C_6D_6) 4.40 (1H, d, *J* 1.0, 1 of C=CH_2), 4.22 (1H, d, *J* 1.0, 1 of C=CH_2), 4.11 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 4.00 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.42 (2H, s, CH_2C≡C), 3.32 (2H, s, CH_2C=C), 1.19-1.12 (42H, m, OsiC*H*(CH_3)$_2$ & SiC*H*(CH_3)$_2$), 0.97 (6H, t, *J* 7.1, OCH_2CH_3); δ_C (75 MHz; C_6D_6) 169.6 (*C*=O), 156.0 ($SiOC=CH_2$), 104.7 (*C*≡C), 93.3 (C=*C*H_2), 83.9 (C≡*C*), 61.4 (OCH_2), 56.8 (O_2CCCO_2), 39.4 (*C*H_2C=C), 24.8 (H_2CC≡CH), 18.9 & 18.3 (OsiCH(*C*H_3)$_2$ & SiCH(*C*H_3)$_2$), 14.1 (OCH_2CH_3), 13.1 (Si*C*H), 11.7 (Si*C*H); *m/z* (FAB pos) 567 (MH^+, 18%), 523 (100), 157 (33); HRMS calculated for $C_{31}H_{59}O_5Si_2$ (MH^+) 567.3901 Found 567.3897.

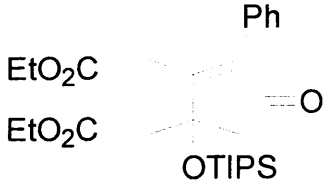
Synthesis of Diethyl 7-phenyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate 367c



n-Butyllithium (1.6 M in hexane, 0.45 mL, 0.73 mmol) was added dropwise to a solution of diisopropylamine (0.10 mL, 0.73 mmol) in THF (2.5 mL) at 0 °C and stirred for 15 minutes. The reaction mixture was cooled to –78 °C, a solution diethyl 7-phenylhept-6-yn-2-one-4,4-dicarboxylate (**361b**, 0.20 g, 0.61 mmol) in THF (2.5 mL) was added dropwise and stirred for 1 h. Triisopropylsilyl triflate (0.20 mL, 0.73 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. The reaction mixture was warmed to rt over 1 h, quenched with sat. aqueous sodium hydrogen carbonate (5 mL) and extracted with diethyl ether (3 x 20 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (Florisil®, Hexane / EtOAc 97 : 3) afforded diethyl 7-phenyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (**367c**, 0.26 g, 87%) as a yellow oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2944s & 2867s (C-H), 1739s (C=O), 1623m, 1491m, 1464s; δ_H (300 MHz; C_6D_6) 7.50-7.44 (2H, m, arom.*H*), 6.99-6.94 (3H, m, arom.*H*), 4.33 (1H, s, 1 of C=CH_2), 4.22 (1H, s, 1 of C=CH_2), 4.16 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.95 (2H, dq, *J* 10.8, 7.1, 2 of OCH_2), 3.61 (2H, s, CH_2C=C), 3.38 (2H, s, H_2CC≡CPh), 1.16-1.11 (21H, m, SiC*H*(CH_3)$_2$), 0.96 (6H, t, *J* 7.2, OCH_2CH_3); δ_C (75 MHz; C_6D_6) 169.9 (*C*=O), 155.9 (SiO*C*=CH_2), 131.9 (arom.*C*H), 128.5 (arom.*C*H), 127.8 (arom.*C*H), 124.1 (arom.C_q), 93.4 (C=*C*H_2), 86.1 & 84.3 (*C*≡*C*), 61.5 (OCH_2), 57.3 (O_2CCCO_2), 39.7 (*C*H_2C=CH_2), 24.4 (H_2CC≡CPh), 18.2 (SiCH(*C*H_3)$_2$), 17.9 (Si*C*H), 14.0 (OCH_2CH_3); *m/z* (CI pos) 488 (10%), 435 (16), 331 (100), 285 (35), 257 (85), 215 (35), 161 (46).

Synthesis of Diethyl 5-triisopropylsilyloxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate 368c



Using the procedure of Mukai *et al.*[91], a solution of diethyl 7-phenyl-2-triisopropylsilyloxyhept-1-en-6-yne-4,4-dicarboxylate (**367c**, 0.10 g, 0.21 mmol) in acetonitrile (1 mL) was added to a solution of dicobalt octacarbonyl (0.11 g, 0.31

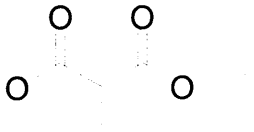
mmol) in acetonitrile (1 mL), at rt under nitrogen, and stirred for 1 h. The resulting reaction mixture was heated to 75 °C overnight.

The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (Florisil®, Petrol 40-60 / EtOAc 95: 5) to obtain diethyl 5-triisopropylsilyloxy-2-phenylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (**368c**, 14 mg, 13%) as a yellow oil.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2926s & 2867s (C-H), 1738s & 1717s (C=O), 1667m (C=C), 1464s, 1386m, 1367s; δ_H (500 MHz; C_6D_6) 7.78-7.76 (2H, m, arom.*H*), 7.20-7.17 (2H, m, arom.*H*), 7.08-7.06 (1H, m, arom.*H*), 4.25 (1H, d, *J* 18.0, 1 of CH_2C=CPh), 4.19 (1H, dq, *J* 10.8, 7.1, 1 of OCH_2), 4.05 (1H, dq, *J* 10.8, 7.1, 1 of OCH_2), 3.80 (1H, dq, *J* 10.8, 7.1, 1 of OCH_2), 3.69 (1H, dq, *J* 10.8, 7.1, 1 of OCH_2), 3.36 (1H, d, *J* 18.0, 1 of CH_2C=CPh), 3.14 (1H, d, *J* 14.0, 1 of CCH_2C(OTIPS)), 2.77 (1H, d, *J* 18.1, 1 of OCCH_2), 2.41 (1H, d, *J* 14.0, 1 of CCH_2C(OTIPS)), 2.36 (1H, d, *J* 18.1, 1 of OCCH_2), 1.04-0.99 (24H, m, SiC*H*(CH_3)$_2$) and OCH_2CH_3), 0.74 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (125 MHz; C_6D_6) 204.0 (*C*=O ketone), 175.5 (*C*=CPh), 171.5 (*C*=O ester), 170.6 (*C*=O ester), 135.1 (C=*C*Ph), 131.0 (arom.C_q), 129.3 (arom.*C*H), 128.8 (arom.*C*H), 128.7 (arom.*C*H), 83.6 (*C*(OTIPS)), 61.88 (O*C*H_2), 61.83 (O*C*H_2), 61.5 (O_2CCCO_2), 48.5 (OC*C*H_2), 47.1 (C*C*H_2C(OTIPS)), 35.1 (*C*H_2C=CPh), 18.4 (SiCH(*C*H_3)$_2$), 18.3 (Si*C*H), 13.9 (OCH_2CH_3), 13.8 (OCH_2CH_3); *m/z* (CI pos) 515 (MH^+, 7%), 471 (30), 369 (17), 341 (93), 157 (57), 131 (100); HRMS calculated for $C_{29}H_{43}O_6Si$ (MH^+) 515.2829 Found 515.2829.

4.2.4 Synthesis of model substrate for ingenol

Synthesis of Diethyl-2-pent-4-enylmalonate 402

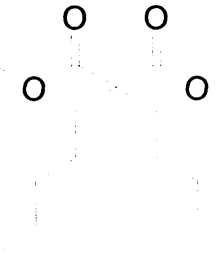


Using the procedure of Marvel and Hager.[89], diethyl malonate (**274**, 1.76 mL, 11.6 mmol) was added dropwise to a solution of sodium ethoxide, prepared by addition of sodium (0.23 g, 10 mmol) in small pieces to ethanol (5 mL), under nitrogen. Once the resultant white precipitate dissolved at rt, 5-bromopent-1-ene (**403**, 1.2 mL, 10 mmol) was added dropwise and the reaction mixture was heated to reflux, overnight.

Ethanol was removed *in vacuo* and the residue was dissolved in H_2O (15 mL). The mixture was extracted with EtOAc (5 x 30 mL), The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Toluene) afforded diethyl-2-pent-4-enylmalonate (**402**, 1.9 g, 83%) as a clear colourless oil.

ν_{max} (neat)/cm^{-1} 3078w (=C-H_2), 2937m & 2864m (C-H), 1732s (C=O), 1641m (C=C), 1447m, 1369m, 1153s; δ_H (500 MHz; $CDCl_3$) 5.77 (1H, ddt, *J* 17.0, 10.3, 6.6, *H*C=CH_2), 5.00 (1H, ddt *J* 17.1, 2.0, 1.7, 1 of HC=CH_2 (*trans*)), 4.95 (1H, ddt *J* 10.3, 1.9, 1.3, 1 of HC=CH_2 (*cis*)), 4.20 (2H, dq, *J* 12.5, 7.2, 2 of OCH_2), 4.17 (4H, dq, *J* 12.4, 7.1, 2 of OCH_2), 3.31 (1H, t, *J* 7.6, CO_2CHCO_2), 2.09-2.05 (2H, m, H_2C=CHCH_2), 1.92-1.87 (2H, m, H_2C=CHCH_2CH_2CH_2), 1.45-1.38 (2H, m, H_2C=CHCH_2CH_2), 1.25 (6H, t, *J* 7.1, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 169.4 (*C*=O), 137.9 (*H*C=CH_2), 115.0 (HC=*C*H_2), 61.3 (O*C*H_2), 51.9 (CO_2*C*HCO_2), 33.2 (H_2C=CH*C*H_2), 28.1 (H_2C=CHCH_2CH_2*C*H_2), 26.5 (H_2C=CHCH_2*C*H_2), 14.0 (*C*H_3); *m/z* (CI pos) 229 (MH^+, 92%), 183 (100), 137 (75); HRMS calculated for $C_{12}H_{21}O_4$ (MH^+) 229.1434 Found 229.1437.

A side product of the reaction diethyl-2,2-dipent-4-enylmalonate (**404**, 0.14 g, 5%) was also isolated as a clear colourless oil.



ν_{max} (neat)/cm^{-1} 3077m (=C-H_2), 2936s & 2844m (C-H), 1730s (C=O), 1641m (C=C), 1446m, 1193s; δ_H (400 MHz; $CDCl_3$) 5.76 (2H, ddt, *J* 16.9, 10.2, 6.7, *H*C=CH_2), 5.00 (2H, ddt *J* 17.1, 1.9, 1.6, 2 of HC=CH_2 (*trans*)), 4.94 (2H, ddt *J* 10.2, 2.0, 1.2, 2 of HC=CH_2 (*cis*)), 4.16 (4H, q, *J* 7.1, OCH_2), 2.07-2.05 (4H, m, H_2C=CHCH_2), 1.89-1.84 (4H, m, H_2C=CHCH_2CH_2CH_2), 1.30-1.23 (4H, m, H_2C=CHCH_2CH_2), 1.22 (6H, t, *J* 7.1, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 171.8 (*C*=O), 138.1 (*H*C=CH_2), 114.9 (HC=*C*H_2), 61.0 (O*C*H_2), 57.4 (CO_2*C*CO_2), 33.8 (H_2C=CH*C*H_2), 31.7 (H_2C=CHCH_2CH_2*C*H_2), 23.3

(H_2C=$CHCH_2CH_2$), 14.1 (CH_3); *m/z* (CI pos) 297 (MH^+, 100%), 251 (90), 149 (85), 113 (40); HRMS calculated for $C_{17}H_{29}O_4$ (MH^+) 297.2060 Found 297.2062.

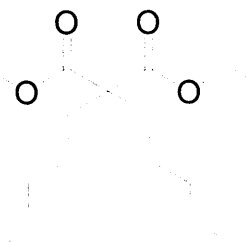
Synthesis of 6-iodohex-1-yne 406[125]

To a solution of sodium iodide (3.9 g, 26 mmol) in acetone (30 mL), under argon, was added 6-chlorohex-1-yne (**405**, 0.52 mL, 4.3 mmol) dropwise. The reaction mixture was heated to reflux overnight.

Acetone was removed *in vacuo* at rt, the residue was dissolved in H_2O (6 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*, at rt, to obtain crude product. Flash chromatography (SiO_2, Hexane) afforded 6-iodohex-1-yne (**406**, 0.77 g, 86%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3296s (C≡C-H), 2941s (C-H), 2120w (C≡C), 1429m, 1211s; δ_H (500 MHz; $CDCl_3$) 3.21 (2H, t, *J* 6.9, CH_2I), 2.23 (2H, td, *J* 6.9, 2.7, HC≡CCH_2), 1.96 (1H, t, *J* 2.7, *H*C≡C), 1.98-1.91 (2H, m, CH_2CH_2I), 1.65-1.62 (2H, m, $CH_2CH_2CH_2I$); δ_C (75 MHz; $CDCl_3$) 83.6 (*C*≡C-H), 68.9 (C≡*C*-H), 32.2 (HC≡CCH_2), 29.1 (CH_2), 17.4 (CH_2), 6.0 (CH_2I); *m/z* (CI pos) 335 (100%, MI^+), 209 (MH^+, 28), 155 (39), 111 (40); HRMS calculated for $C_6H_{10}I$ (MH^+) 208.9827 Found 208.9829.

Synthesis of Diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate 401

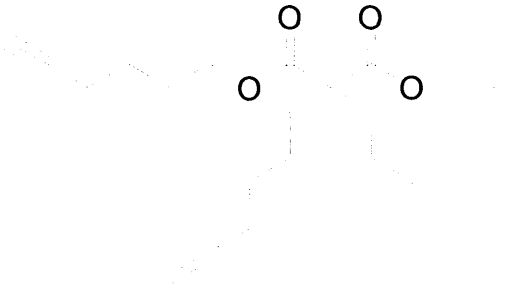


To a suspension of sodium hydride (60% dispersion in oil, 68 mg, 1.7 mmol) in DMF (1.2 mL) at 0 °C, under argon, was added a solution of diethyl-2-pent-4-enylmalonate (**402**, 0.30 g, 1.3 mmol) in DMF (3.5 mL) and stirred for 30 minutes. A solution of 6-iodohex-1-yne (**406**, 0.36 g, 1.7 mmol) in DMF (3.5 mL) was added dropwise to reaction mixture, which was stirred at rt for 3 h.

The reaction mixture was quenched with H_2O (200 mL) and extracted with EtOAc (4 x 200 mL). The combined organic extracts were washed with brine (400 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Petrol 40-60 / EtOAc 98 : 2) afforded diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (**401**, 0.35 g, 86%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3296s (C≡C-H), 3076w (=C-H$_2$), 2937s (C-H), 2118w (C≡C), 1728s (C=O), 1641s (C=C), 1447s, 1367s, 1175s, 1097s; δ_H (500 MHz; $CDCl_3$) 5.76 (1H, ddt, *J* 17.1, 10.2, 6.6, *H*C=CH$_2$), 5.00 (1H, ddt *J* 17.1, 1.9, 1.6, 1 of HC=C*H*$_2$ (*trans*)), 4.95 (1H, ddt *J* 10.2, 1.9, 1.3, 1 of HC=C*H*$_2$ (*cis*)), 4.16 (4H, q, *J* 7.1, OC*H*$_2$), 2.18 (2H, td, *J* 7.1, 2.6, HC≡CC*H*$_2$), 2.07-2.02 (2H, m, H$_2$C=CHC*H*$_2$), 1.91 (1H, t, *J* 2.6, *H*C≡C), 1.89-1.85 (4H, m, H$_2$C=CHCH$_2$CH$_2$C*H*$_2$ and HC≡CCH$_2$CH$_2$CH$_2$C*H*$_2$), 1.55-1.49 (2H, m, HC≡CCH$_2$C*H*$_2$), 1.30-1.23 (4H, m, H$_2$C=CHCH$_2$C*H*$_2$ and HC≡CCH$_2$CH$_2$C*H*$_2$), 1.23 (6H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 171.7 (*C*=O), 138.1 (H*C*=CH$_2$), 114.9 (HC=*C*H$_2$), 84.0 (*C*≡C-H), 68.4 (C≡*C*-H), 61.0 (O*C*H$_2$), 57.3 (CO_2CCO_2), 33.8 (H$_2$C=CH*C*H$_2$), 31.62 & 31.57 (H$_2$C=CHCH$_2$CH$_2$*C*H$_2$ and HC≡CCH$_2$CH$_2$CH$_2$*C*H$_2$), 28.5 (HC≡CCH$_2$*C*H$_2$), 23.4 & 22.9 (H$_2$C=CHCH$_2$*C*H$_2$ and HC≡CCH$_2$CH$_2$*C*H$_2$), 18.0 (HC≡*C*CH$_2$), 14.1 (*C*H$_3$); *m/z* (CI pos) 309 (MH$^+$, 41%), 263 (100), 217 (60), 189 (50), 161 (58); HRMS calculated for $C_{18}H_{29}O_4$ (MH$^+$) 309.2060 Found 309.2062.

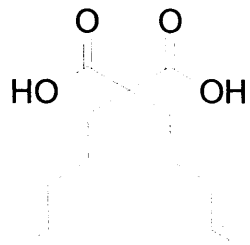
A side product of the reaction, Ethylhex-5-ynyl-2-hex-5-ynyl-2-pent-4-enylmalonate (**407**, 0.02 g, 4%) was also isolated.



ν_{max} (neat)/cm^{-1} 3308s (C≡C-H), 3078w (=C-H$_2$), 2941s (C-H), 2257m (C≡C), 2120w (C≡C), 1728s (C=O), 1641m (C=C), 1460s, 1252s, 1097s; δ_H (500 MHz; $CDCl_3$) 5.76 (1H, ddt, *J* 16.9, 10.2, 6.6, *H*C=CH$_2$), 5.02 (1H, br dd *J* 17.1, 1.7, 1 of HC=C*H*$_2$ (*trans*)), 4.96 (1H, br d *J* 10.2, 1 of HC=C*H*$_2$ (*cis*)), 4.19 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.14 (2H, t, *J* 6.4, OC*H*$_2$), 2.21 (2H, td, *J* 7.1, 2.6, HC≡CC*H*$_2$ of hex-5-ynyl ester), 2.19 (2H, td, *J* 7.1, 2.6, HC≡CC*H*$_2$), 2.07-2.03 (2H, m, H$_2$C=CHC*H*$_2$), 1.95 (1H, t, *J* 2.6, *H*C≡C of hex-5-ynyl ester), 1.92 (1H, t, *J* 2.6, *H*C≡C), 1.90-1.86 (4H, m, H$_2$C=CHCH$_2$CH$_2$C*H*$_2$ and HC≡CCH$_2$CH$_2$CH$_2$C*H*$_2$), 1.77-1.72 (2H, m, HC≡CCH$_2$CH$_2$C*H*$_2$ of hex-5-ynyl ester), 1.60-1.55 (2H, m, HC≡CCH$_2$C*H*$_2$ of hex-5-ynyl ester), 1.55-1.50 (2H, m, HC≡CCH$_2$C*H*$_2$), 1.31-1.20 (4H, m, H$_2$C=CHCH$_2$C*H*$_2$ and HC≡CCH$_2$CH$_2$C*H*$_2$), 1.24 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 171.8 & 171.7 (2 x *C*=O), 138.0

($HC{=}CH_2$), 115.0 ($HC{=}CH_2$), 84.0 & 83.6 (2 x $C{\equiv}C$-H), 68.8 & 68.4 (2 x $C{\equiv}C$-H), 64.5 (OCH_2), 61.1 (OCH_2CH_3), 57.4 (CO_2CCO_2), 33.8 ($H_2C{=}CHCH_2$), 31.70 & 31.67 ($H_2C{=}CHCH_2CH_2CH_2$ and $HC{\equiv}CCH_2CH_2CH_2CH_2$), 28.5 ($HC{\equiv}CCH_2CH_2$), 27.5 ($HC{\equiv}CCH_2CH_2CH_2$ of hex-5-ynyl ester), 24.8 ($HC{\equiv}CCH_2CH_2$ of hex-5-ynyl ester), 23.3 & 22.7 ($H_2C{=}CHCH_2CH_2$ and $HC{\equiv}CCH_2CH_2CH_2$), 18.1 & 18.0 (2 x $HC{\equiv}CCH_2$), 14.1 (CH_3); *m/z* (FAB pos) 361 (MH^+, 100%), 338 (35), 263 (9); HRMS calculated for $C_{22}H_{33}O_4$ (MH^+) 361.2379 Found 361.2384.

Synthesis of 2-Hex-5-ynyl-2-pent-4-enylmalonic acid 400

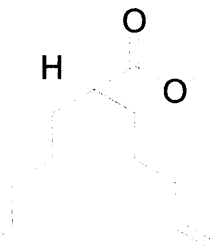


Using the procedure of Pugia *et al.*[126], diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (**401**, 0.20 g, 0.65 mmol) in 50% aqueous NaOH (4 mL) was heated to reflux for 2 days.

The reaction mixture was cooled, washed with diethyl ether (2 x 20 mL) and ethereal extracts discarded. The aqueous layer was acidified to pH 1 with 2M HCl and extracted with diethyl ether (5 x 50 mL). The combined organic extracts were washed successively with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain crude product. Recrystallisation (ether / hexane) yielded 2-hex-5-ynyl-2-pent-4-enylmalonic acid (**400**, 55 mg, 34%) as a white crystalline solid.

m.p.: 115 °C; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3296s (C≡C-H), 3000-2610 br s (O-H + C-H), 2130w (C≡C), 1697s (C=O), 1639s (C=C), 1435s, 1300s, 1182s; δ_H (500 MHz; CD_3OD) 5.79 (1H, ddt, *J* 17.0, 10.2, 6.7, $HC{=}CH_2$), 5.00 (1H, ddt *J* 17.1, 3.6, 1.6, 1 of $HC{=}CH_2$ (*trans*)), 4.94 (1H, ddt *J* 10.2, 2.2, 1.2, 1 of $HC{=}CH_2$ (*cis*)), 2.19 (1H, t, *J* 2.6, $HC{\equiv}C$), 2.18-2.16 (2H, m, $HC{\equiv}CCH_2$), 2.08-2.04 (2H, m, $H_2C{=}CHCH_2$), 1.87-1.83 (4H, m, $H_2C{=}CHCH_2CH_2CH_2$ and $HC{\equiv}CCH_2CH_2CH_2CH_2$), 1.53-1.48 (2H, m, $HC{\equiv}CCH_2CH_2$), 1.36-1.27 (4H, m, $HC{\equiv}CCH_2CH_2CH_2$ and $H_2C{=}CHCH_2CH_2$); δ_C (125 MHz; CD_3OD) 175.6 (C=O), 139.4 ($HC{=}CH_2$), 115.3 ($HC{=}CH_2$), 84.7 ($C{\equiv}C$-H), 69.7 ($C{\equiv}C$-H), 58.4 (CO_2CCO_2), 35.0 ($H_2C{=}CHCH_2$), 33.26 & 33.25 ($H_2C{=}CHCH_2CH_2CH_2$ and $HC{\equiv}CCH_2CH_2CH_2CH_2$), 29.8 ($HC{\equiv}CCH_2CH_2$), 24.7 & 24.2 ($H_2C{=}CHCH_2CH_2$ and $HC{\equiv}CCH_2CH_2CH_2$), 18.8 ($HC{\equiv}CCH_2$).

Synthesis of Ethyl-2-pent-4-enyl-2-hex-5-ynoate 408

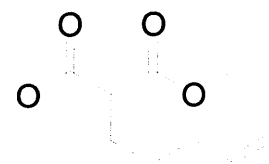


Using the procedure of Krapcho *et al.*[105], a solution of diethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (**401**, 2.32 g, 7.52 mmol), lithium chloride (0.64 g, 15 mmol) and H_2O (0.14 mL, 7.5 mmol) in DMSO (12.5 mL) was heated to reflux overnight.

The reaction mixture was cooled, diluted with H_2O (60 mL) and extracted with EtOAc (5 x 150 mL). The combined organic extracts were washed with brine (600 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain crude product. Flash chromatography (SiO_2, Petrol 40-60 / EtOAc 98 : 2) afforded ethyl-2-pent-4-enyl-2-hex-5-ynoate (**408**, 1.41 g, 79%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3312s (C≡C-H), 3078s (=C-H_2), 2739 br s (C-H), 2120m (C≡C), 1734s (C=O), 1641s (C=C); δ_H (500 MHz; $CDCl_3$) 5.73 (1H, ddt, *J* 17.1, 10.2, 6.7, *H*C=CH_2), 4.95 (1H, ddt *J* 17.1, 2.0, 1.6, 1 of HC=CH_2 (*trans*)), 4.90 (1H, ddt *J* 10.2, 2.0, 1.2, 1 of HC=CH_2 (*cis*)), 4.10 (2H, q, *J* 7.2, OCH_2), 2.29 (1H, tt, *J* 8.9, 5.1, *H*CCO_2), 2.13 (2H, td, *J* 7.1, 2.6, HC≡CCH_2), 2.03-1.98 (2H, m, H_2C=CHCH_2), 1.89 (1H, t, *J* 2.7, *H*C≡C), 1.56-1.54 (2H, m, H_2C=CH$CH_2CH_2CH_2$), 1.51-1.46 (2H, m, HC≡CCH_2CH_2), 1.43-1.38 (4H, m, HC≡C$CH_2CH_2CH_2$ and HC≡C$CH_2CH_2CH_2CH_2$), 1.37-1.30 (2H, m, H_2C=CHCH_2CH_2), 1.22 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (125 MHz; $CDCl_3$) 176.1 (*C*=O), 138.3 (H*C*=CH_2), 114.5 (HC=*C*H_2), 84.2 (*C*≡C-H), 68.2 (C≡*C*-H), 59.9 (O*C*H_2), 45.3 (H*C*CO_2), 33.5 (H_2C=CH*C*H_2), 31.79 & 31.76 (H_2C=CHCH_2CH_2*C*H_2 and HC≡C$CH_2CH_2CH_2$*C*H_2), 28.2 (HC≡CCH_2*C*H_2), 26.5 & 26.4 (H_2C=CHCH_2*C*H_2 and HC≡CCH_2CH_2*C*H_2), 18.1 (HC≡*C*CH_2), 14.2 (*C*H_3); *m/z* (CI pos) 237 (MH^+, 100%), 209 (11), 163 (14); HRMS calculated for $C_{15}H_{25}O_2$ (MH^+) 237.1855 Found 237.1853.

Synthesis of Dimethyl-2-pent-4-enylmalonate 412



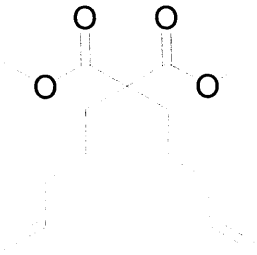
Using the procedure of Marvel and Hager *et al.*[89], dimethyl malonate (**409**, 1.2 mL, 11.6 mmol) was added dropwise to a solution of sodium methoxide, prepared by addition of sodium (0.23 g, 10.1 mmol) in small pieces to methanol (5 mL) under

nitrogen. Once the resultant white precipitate dissolved at rt, 5-bromopent-1-ene (**403**, 1.2 mL, 10.1 mmol) was added dropwise and the reaction mixture was heated to reflux, overnight.

Methanol was removed *in vacuo*, the residue was dissolved in H_2O (15 mL) and extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Toluene) afforded dimethyl-2-pent-4-enylmalonate (**412**, 1.15 g, 57%) as a clear colourless oil.

ν_{max} (neat)/cm^{-1} 3080w (=C-H_2), 2955s (C-H), 1734s (C=O), 1641s (C=C), 1437s, 1344s, 1155s; δ_H (500 MHz; $CDCl_3$) 5.72 (1H, ddt, *J* 17.0, 10.2, 6.7, *H*C=CH_2), 4.97 (1H, ddt *J* 17.1, 1.7, 1.7, 1 of HC=CH_2 (*trans*)), 4.91 (1H, ddt *J* 10.2, 1.9, 1.2, 1 of HC=CH_2 (*cis*)), 3.68 (6H, s, OCH_3), 3.32 (1H, t *J* 7.5, CO_2CHCO_2), 2.06-2.01 (2H, m, H_2C=CHCH_2), 1.89-1.84 (2H, m, H_2C=CHCH_2CH_2CH_2), 1.40-1.34 (2H, m, H_2C=CHCH_2CH_2); δ_C (125 MHz; $CDCl_3$) 169.7 (*C*=O), 137.7 (*H*C=CH_2), 114.9 (HC=*C*H_2), 52.3 (O*C*H_3), 51.4 CO_2CHCO_2), 33.1 (H_2C=CH*C*H_2), 28.1 (H_2C=CHCH_2CH_2*C*H_2), 26.4 (H_2C=CHCH_2*C*H_2); *m/z* (CI pos) 201 (MH^+, 100%), 169 (80), 137 (90), 108 (50); HRMS calculated for $C_{10}H_{17}O_4$ (MH^+) 201.1127 Found 201.1122.

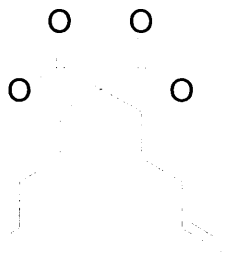
A side product of the reaction, dimethyl-2,2-dipent-4-enylmalonate (**413**, 0.05 g, 12%), was also isolated as a clear colourless oil.



ν_{max} (neat)/cm^{-1} 3077w (=C-H_2), 2953s & 2927m (C-H), 1733s (C=O), 1641m (C=C), 1460m, 1436m, 1259s, 1197s; δ_H (500 MHz; $CDCl_3$) 5.75 (2H, ddt, *J* 17.2, 10.2, 6.7, *H*C=CH_2), 5.00 (2H, ddt *J* 17.2, 2.1, 1.7, 1 of HC=CH_2 (*trans*)), 4.95 (2H, ddt *J* 10.2, 2.1, 1.3, 1 of HC=CH_2 (*cis*)), 3.70 (6H, s, OCH_3), 2.06-2.02 (4H, m, H_2C=CHCH_2), 1.89-1.85 (4H, m, H_2C=CHCH_2CH_2CH_2), 1.27-1.20 (4H, m, H_2C=CHCH_2CH_2); δ_C (125 MHz; $CDCl_3$) 172.2 (*C*=O), 137.8 (*H*C=CH_2), 115.0 (HC=*C*H_2), 57.5 (CO_2CCO_2),

52.3 (OCH_3), 33.7 (H_2C=$CHCH_2$), 31.9 (H_2C=$CHCH_2CH_2CH_2$), 23.4 (H_2C=$CHCH_2CH_2$); *m/z* (CI pos) 269 (MH^+, 100%), 237 (50), 205 (20), 149 (10); HRMS calculated for $C_{10}H_{17}O_4$ (MH^+) 269.1753 Found 269.1758.

Synthesis of Dimethyl-2-hex-5-ynyl-2-pent-4-enylmalonate 414

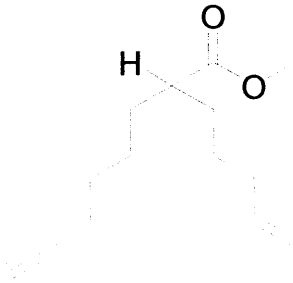


To a suspension of sodium hydride (60% dispersion in oil, 0.21 g, 5.2 mmol) in DMF (2 mL) at 0 °C, under argon, was added a solution of dimethyl-2-pent-4-enylmalonate (**412**, 0.80 g, 4.0 mmol) in DMF (8 mL). A solution of 6-iodohex-1-yne (**406**, 1.0 g, 4.8 mmol) in DMF (10 mL) was added dropwise to the reaction mixture, which was stirred at rt overnight.

The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (4 x 150 mL). The combined organic extracts were washed with brine (450 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Petrol 40-60 / EtOAc 98 : 2) afforded dimethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (**414**, 1.09 g, 98%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3296s (C≡C-H), 3077w (=C-H_2), 2951s & 2702s (C-H), 2116w (C≡C), 1736s (C=O), 1639m (C=C), 1435s, 1171s, 1099m; δ_H (500 MHz; $CDCl_3$) 5.71 (1H, ddt, *J* 17.1, 10.3, 6.5, *H*C=CH_2), 4.96 (1H, ddt *J* 17.2, 1.9, 1.6, 1 of HC=CH_2 (*trans*)), 4.91 (1H, ddt *J* 10.3, 1.9, 1.2, 1 of HC=CH_2 (*cis*)), 3.66 (6H, s, OCH_3), 2.14 (2H, td, *J* 7.1, 2.7, HC≡CCH_2), 2.02-1.98 (2H, m, H_2C=CHCH_2), 1.88 (1H, t, *J* 2.7, *H*C≡C), 1.85-1.81 (4H, m, H_2C=$CHCH_2CH_2CH_2$ and HC≡$CCH_2CH_2CH_2CH_2$), 1.51-1.45 (2H, m, HC≡$CCH_2CH_2CH_2$), 1.25-1.17 (4H, m, H_2C=$CHCH_2CH_2$ and HC≡$CCH_2CH_2CH_2CH_2$); δ_C (125 MHz; $CDCl_3$) 172.0 (*C*=O), 137.9 (H*C*=CH_2), 114.9 (HC=*C*H_2), 83.8 (*C*≡C-H), 68.4 (C≡*C*-H), 57.3 (CO_2CCO_2), 52.2 (OCH_3), 33.6 (H_2C=$CHCH_2$), 31.8 & 31.7 (H_2C=$CHCH_2CH_2CH_2$ and HC≡$CCH_2CH_2CH_2CH_2$), 28.3 (HC≡CCH_2CH_2), 23.2 & 22.9 (H_2C=$CHCH_2CH_2$ and HC≡$CCH_2CH_2CH_2$), 17.9 (HC≡CCH_2); *m/z* (CI pos) 281 (MH^+, 48%), 249 (100), 217 (50), 189 (45), 161 (40), 95 (41); HRMS calculated for $C_{16}H_{25}O_4$ (MH^+) 281.1753 Found 281.1758.

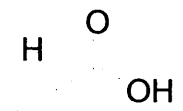
Synthesis of Methyl-2-pent-4-enyl-2-hex-5-ynoate 415



Using the procedure of Krapcho *et al.*[105], a solution of dimethyl-2-hex-5-ynyl-2-pent-4-enylmalonate (**414**, 0.70 g, 2.5 mmol), lithium chloride (0.21 g, 5.0 mmol) and H_2O (50μL, 2.50 mmol) in DMSO (4.2 mL) was heated to reflux for 7 h. The reaction mixture was cooled, diluted with H_2O (20 mL) and extracted with EtOAc (6 x 80 mL). The combined organic extracts were washed with brine (350 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain crude product. Flash chromatography (SiO_2, Petrol 40-60 / EtOAc 98 : 2) afforded methyl-2-pent-4-enyl-2-hex-5-ynoate (**415**, 0.26 g, 48%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3306s (C≡C-H), 3077w (=C-H_2), 2943s & 2864s (C-H), 2118w (C≡C), 1736s (C=O), 1641m (C=C), 1435m, 1159s; δ_H (500 MHz; $CDCl_3$) 5.75 (1H, ddt, *J* 17.0, 10.2, 6.70, *H*C=CH_2), 4.97 (1H, ddt *J* 17.1, 1.9, 1.7, 1 of HC=CH_2 (*trans*)), 4.92 (1H, ddt *J* 10.2, 2.0, 1.2, 1 of HC=CH_2 (*cis*)), 3.65 (3H, s, OCH_3), 2.34 (1H, tt, *J* 8.9, 5.2, *H*CCO_2), 2.15 (2H, td, *J* 7.2, 2.6, HC≡CCH_2), 2.05-2.01 (2H, m, H_2C=CHCH_2), 1.91 (1H, t, *J* 2.6, *H*C≡C), 1.65-1.58 (2H, m, H_2C=CHCH_2CH_2CH_2), 1.50-1.37 (4H, m, HC≡CCH_2CH_2 and HC≡CCH_2CH_2CH_2CH_2), 1.36-1.32 (4H, m, H_2C=CHCH_2CH_2 and HC≡CCH_2CH_2CH_2); δ_C (125 MHz; $CDCl_3$) 176.6 (*C*=O), 138.3 (H*C*=CH_2), 114.6 (HC=*C*H_2), 84.2 (*C*≡C-H), 68.3 (C≡*C*-H), 51.5 (O*C*H_3), 45.3 (H*C*CO_2), 33.5 (H_2C=CH*C*H_2), 31.81 & 31.79 (H_2C=CHCH_2CH_2*C*H_2 and HC≡CCH_2CH_2CH_2*C*H_2), 28.3 (HC≡CCH_2*C*H_2), 26.6 & 26.5 (H_2C=CHCH_2*C*H_2 and HC≡CCH_2CH_2*C*H_2), 18.2 (HC≡C*C*H_2); *m/z* (CI pos) 223 (MH^+, 100%), 163 (55), 81 (25); HRMS calculated for $C_{14}H_{23}O_2$ (MH^+) 223.1698 Found 223.1696.

Synthesis of 2-Pent-4-enyloct-7-ynoic acid 399



Method 1

Using the procedure of Rosini *et al.*[129], a solution of ethyl-2-pent-4-enyl-2-hex-5-ynoate (**408**, 0.20 g, 0.85 mmol) in 2M potassium hydroxide in ethanol (0.55 mL, 1.1 mmol) was heated to reflux overnight.

Ethanol was removed *in vacuo* and the residue dissolved in H_2O (8 mL). The solution was washed with diethyl ether (3 x 20 mL) to remove traces of unreacted ester. The aqueous layer was acidified to pH 1 with 6M HCl and then extracted with diethyl ether (5 x 20 mL). The combined organic extracts were successively washed with H_2O (80 mL) and brine (80 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain crude product. Flash chromatography (SiO_2, Hexane / Acetone 4 : 1) afforded 2-pent-4-enyloct-7-ynoic acid (**399**, 0.16 g, 96%) as a colourless oil.

Method 2

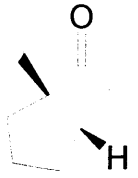
Using the procedure of Rosini *et al.*[129], a solution of methyl-2-pent-4-enyl-2-hex-5-ynoate (**415**, 0.2 g, 0.9 mmol) in 2M potassium hydroxide in methanol (0.58 mL, 1.2 mmol) was heated to reflux overnight.

Methanol was removed *in vacuo* and the residue dissolved in H_2O (8 mL). This solution was washed with diethyl ether (3 x 20 mL) to remove traces of unreacted ester. The aqueous layer was acidified to pH 1 with 6M HCl and then extracted with diethyl ether (5 x 20 mL). The combined organic extracts were successively washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain crude product. Flash chromatography (SiO_2, Hexane / Acetone 4 : 1) afforded 2-pent-4-enyloct-7-ynoic acid (**399**, 0.14 g, 75%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3304s (C≡C-H), 3100br (O-H), 2855s (C-H), 2118w (C≡C), 1705s (C=O), 1641s (C=C), 1418s, 1232s; δ_H (500 MHz; $CDCl_3$) 11.73 (1H, br s, O*H*), 5.76

(1H, ddt, *J* 17.0, 10.3, 6.7, *H*C=CH_2), 4.99 (1H, ddt *J* 17.1, 1.9, 1.6, 1 of HC=CH_2 (*trans*)), 4.94 (1H, ddt *J* 10.3, 2.0, 1.3, 1 of HC=CH_2 (*cis*)), 2.35 (1H, tt, *J* 8.6, 5.0, *H*CCO_2), 2.17 (2H, td, *J* 7.0, 2.7, HC≡CCH_2), 2.07-2.02 (2H, m, H_2C=CHCH_2), 1.92 (1H, t, *J* 2.7, *H*C≡C), 1.67-1.60 (2H, m, H_2C=CHCH_2CH_2CH_2), 1.56-1.36 (8H, m, H_2C=CHCH_2CH_2, HC≡CCH_2CH_2CH_2CH_2, HC≡CCH_2CH_2CH_2 and HC≡CCH_2CH_2); δ_C (125 MHz; $CDCl_3$) 183.0 (*C*=O), 138.2 (H*C*=CH_2), 114.7 (HC=*C*H_2), 84.1 (*C*≡C-H), 68.4 (C≡*C*-H), 45.2 (H*C*CO_2), 33.5 (H_2C=CH*C*H_2), 31.43 & 31.40 (H_2C=CHCH_2CH_2*C*H_2 and HC≡CCH_2CH_2CH_2*C*H_2), 28.2 (HC≡CCH_2*C*H_2), 26.4 & 26.3 (H_2C=CHCH_2*C*H_2 and HC≡CCH_2CH_2*C*H_2), 18.1 (HC≡*C*CH_2); *m/z* (CI pos) 209 (MH^+, 96%), 191 (48), 163 (100), 123 (73); HRMS calculated for $C_{13}H_{21}O_2$ (MH^+) 209.1542 Found 209.1538.

Synthesis of 5-Hex-5-ynyl-bicyclo[3.2.0]heptan-6-one 396



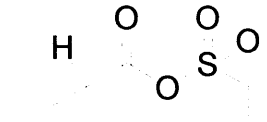
Using the procedure of Sinder *et al.*[130], a solution of 2-pent-4-enyloct-7-ynoic acid (**399**, 0.57 g, 2.7 mmol) in benzene (5.7 mL) was added slowly to a suspension of sodium hydride (60% dispersion in oil, 0.16 g, 4.1 mmol) in benzene (7.0 mL) at 0 °C under argon and stirred for 15 min. Oxalyl chloride (1.20 mL, 13.7 mmol) was added dropwise and the resultant reaction mixture warmed to rt and then heated at 60 °C for 1 h. The reaction mixture was cooled and concentrated *in vacuo*. The resultant mixture of acid chloride and sodium chloride was taken up in toluene (7.3 mL) and added dropwise to a solution of triethylamine (3.8 mL, 27 mmol) in toluene (27 mL) at reflux and heated to reflux, under argon, overnight.

The reaction mixture was cooled to rt, filtered through Celite® and concentrated *in vacuo* to obtain the crude product. Flash chromatography (SiO_2, Hexane / Toluene 3 : 2) afforded 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (**396**, 0.34 g, 65%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 3292s (C≡C-H), 2978s (C-H), 2100w (C≡C), 1771s (C=O), 1450m, 1387m, 1240m, 1067m; δ_H (500 MHz; $CDCl_3$) 3.09 (1H, dd, *J* 18.5, 9.7, 1 of OCCH_2), 2.58-2.54 (1H, m, OCCH_2C*H*), 2.41 (1H, dd, *J* 18.5, 4.6, 1 of OCCH_2), 2.16 (2H, td, *J* 7.1, 2.7, HC≡CCH_2), 1.98 (1H, dd, *J* 12.9, 6.3, 1 of OCCCH_2), 1.92 (1H, t, *J* 2.7, *H*C≡C), 1.85-1.75 (3H, m, 1 of OCCH_2CHCH_2CH_2, HC≡CCH_2CH_2CH_2CH_2), 1.70-1.48

(6H, m, 1 of $OCCH_2CHCH_2CH_2$, 1 of $OCCH_2CHCH_2$, $HC{\equiv}CCH_2CH_2$, $HC{\equiv}CCH_2CH_2CH_2CH_2$), 1.41-1.33 (2H, m, 1 of $OCCCH_2$, 1 of $OCCH_2CHCH_2$); δ_C (125 MHz; $CDCl_3$) 218.0 (*C*=O), 84.2 (*C*≡C-H), 75.7 (OC*C*), 68.3 (C≡*C*-H), 49.2 ($OCCH_2$), 35.3 ($OCCCH_2$), 33.9 ($OCCH_2CH$), 32.6 ($HC{\equiv}CCH_2CH_2CH_2CH_2$), 32.5 ($HC{\equiv}CCH_2CH_2CH_2$), 28.8 ($HC{\equiv}CCH_2CH_2$), 24.9 ($OCCH_2CHCH_2CH_2$), 24.7 ($OCCH_2CHCH_2$), 18.2 ($HC{\equiv}CCH_2$); *m/z* (CI pos) 257 (100%), 243 (35), 191 (MH^+, 31), 173 (41), 149 (70), 121 (40); HRMS calculated for $C_{13}H_{19}O$ (MH^+) 191.1436 Found 191.1437.

Synthesis of 7-(4-Toluenesulfonyloxycarbonyl)dodec-11-en-1-yne 416



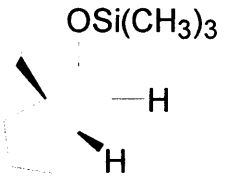
Using the procedure of Corey *et al.*[131], triethylamine (0.40 mL, 2.9 mmol) was added to a solution of 2-pent-4-enyloct-7-ynoic acid (**399**, 0.10 g, 0.48 mmol) and *para*-toluenesulfonyl chloride (0.28 g, 1.4 mmol) in benzene (6.7 mL) under argon and heated to reflux fo 3 h.

The reaction mixture was cooled, filtered through Celite® to remove the white precipitate and concentrated *in vacuo* to obtain crude product. Flash chromatography (SiO_2, Hexane / Acetone 95 : 5) afforded 7-(4-toluenesulfonyloxycarbonyl)dodec-11-en-1-yne (**416**, 0.17 g, 99%) as a yellow oil.

ν_{max} (neat)/cm^{-1} 3304s (C≡C-H), 3170w (=C-H_2), 2941s & 2862s (C-H), 2190w (C≡C), 1809s (C=O), 1705s (C=O of carboxylic acid **399**), 1641w (C=C), 1595 (C=C aromatic), 1460 (C=C aromatic), 1379s, 1175s, 1026m; δ_H (400 MHz; $CDCl_3$) 7.92 (2H, d, *J* 8.4, PhC-*H*), 7.40 (2H, d, *J* 8.4, PhC-*H*), 5.76 (1H, ddt, *J* 17.0, 10.2, 6.6, *H*C=CH_2), 5.03-4.98 (1H, m, 1 of HC=CH_2), 4.97-4.94 (1H, m, 1 of HC=CH_2), 2.48 (3H, s, CH_3), 2.43 (1H, tt, *J* 8.9, 5.3, *H*CCO_2), 2.19 (2H, td, *J* 6.7, 2.5, HC≡CCH_2), 2.09-2.03 (2H, m, H_2C=CHCH_2), 1.94 (1H, t, *J* 2.6, *H*C≡C), 1.73-1.61 (2H, m, H_2C=$CHCH_2CH_2CH_2$), 1.57-1.40 (8H, m, H_2C=$CHCH_2CH_2$, $HC{\equiv}CCH_2CH_2CH_2CH_2$, $HC{\equiv}CCH_2CH_2CH_2$ and $HC{\equiv}CCH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 171.6 (*C*=O), 146.8 (arom.C_q), 141.6 (arom.C_q), 138.0 (H*C*=CH_2), 130.2 (arom.*C*H), 127.0 (arom.*C*H), 115.0 (HC=*C*H_2), 84.1 (*C*≡C-H), 68.5 (C≡*C*-H), 46.3 (H*C*CO_2), 33.5 (H_2C=*C*H_2), 31.1 & 31.0 (H_2C=$CHCH_2CH_2CH_2$ and $HC{\equiv}CCH_2CH_2CH_2CH_2$), 28.2 ($HC{\equiv}CCH_2CH_2$), 26.3 & 26.2 ($H_2C$=$CHCH_2CH_2$

and HC≡CCH$_2$CH$_2$*C*H$_2$), 21.8 *C*H$_3$), 18.2 (HC≡C*C*H$_2$); *m/z* (EI pos) 333 (8%), 277 (14), 217 (13), 191 (91), 173 (82), 155 (ArSO$_2^+$, 94), 121 (100).

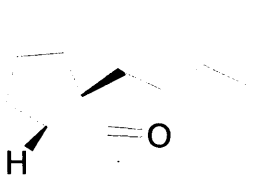
Synthesis of 1-Hex-5-ynyl-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene 417



Using the procedure of Wu *et al.*[132], lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.55 mL, 0.55 mmol) was added dropwise to a stirred solution of 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (**396**, 0.10 g, 0.53 mmol) in THF (1 mL) at –78 °C under argon and stirred for 45 minutes, then trimethylchlorosilane (80 μL, 0.63 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min and then allowed to warm to rt. The reaction mixture was concentrated *in vacuo* and dissolved in hexane (5 mL), to precipitate out lithium salts, filtered through cotton wool and concentrated *in vacuo* at rt to obtain 1-hex-5-ynyl-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (**417**, 0.13 g, 93%) as a pale yellow oil, contaminated with trimethylsilyl impurities, which was used without further purification.

ν_{max} (neat)/cm^{-1} 3313m (C≡C-H), 3080w (=C-H), 2938s (C-H), 1619s (C=C), 1351m, 1254s, 1194s; δ_H (500 MHz; C$_6$D$_6$) 4.34 (1H, s, C=C*H*), 2.41 (1H, d, *J* 6.2, C=CHC*H*), 1.99 (2H, td, *J* 7.1, 2.7, HC≡CC*H*$_2$), 1.94-1.84 (1H, m, 1 of C=CHCHCH$_2$C*H*$_2$), 1.79 (1H, t, *J* 2.7, *H*C≡C), 1.76-1.74 (1H, m, 1 of C=CHCHCH$_2$CH$_2$C*H*$_2$), 1.69-1.65 (1H, m, 1 of C=CHCHCH$_2$C*H*$_2$), 1.62-1.45 (5H, m, 1of C=CHCHC*H*$_2$, HC≡CCH$_2$CH$_2$CH$_2$*C*H$_2$ and HC≡CCH$_2$CH$_2$C*H*$_2$), 1.40-1.39 (2H, m, HC≡CCH$_2$C*H*$_2$), 1.28-1.20 (1H, m, 1 of C=CHCHC*H*$_2$), 0.99-0.93 (1H, m, 1 of C=CHCHCH$_2$CH$_2$C*H*$_2$), 0.16 (9H, s, OSi(C*H*$_3$)$_3$); δ_C (125 MHz; C$_6$D$_6$) 152.0 (O*C*=CH), 100.8 (C=*C*H), 84.5 (*C*≡C-H), 68.7 (C≡*C*-H), 61.7 (SiO*C*C), 43.1 (C=CCH*C*H), 34.2 & 25.5 (HC≡CCH$_2$CH$_2$*C*H$_2$CH$_2$), 29.7 (C=CHCHCH$_2$CH$_2$*C*H$_2$), 29.5 (HC≡CCH$_2$*C*H$_2$), 27.5 (C=CHCH*C*H$_2$), 24.2 (C=CHCHCH$_2$*C*H$_2$), 18.6 (HC≡C*C*H$_2$), -0.2 (OSi(*C*H$_3$)$_3$); *m/z* (ES pos) 285 (MNa$^+$, 100%), 213 (35); HRMS calculated for C$_{16}$H$_{26}$ONa (MNa$^+$) 285.1645 Found 285.1648.

Synthesis of 1-(6-Trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one 419



Method 1

Using the procedure of Sugihara *et al.*[29], a solution of 1-hex-5-ynyl-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (**417**, 0.13 g, 0.51 mmol) in 1,2-dichloroethane (3.1 mL) was added to a solution of dicobalt octacarbonyl (0.25 g, 0.73 mmol) in 1,2-dichloroethane (2 mL), under argon at rt. The reaction mixture was stirred at rt for 1 h. *n*-Butyl methyl sulfide (0.22 mL, 1.8 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled, a solution of *para*-toluenesulfonic acid monohydrate (0.19 g, 1.02 mmol) in methanol (4 mL) was added and the mixture was stirred at rt for 2 h.

The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, gradient elution, EtOAc / Hexane 5 : 95 to 50 : 50) to afford 1-(6-Trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one (**419**, 9.4 mg, 5% (from cyclobutanone **396**) as a colourless oil.

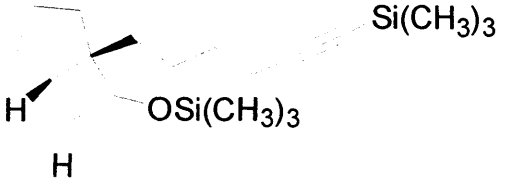
Method 2

Using the procedure of Wu *et al.*[132]. lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.28 mL, 0.28 mmol) was added dropwise to a stirred solution of 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (**396**, 50 mg, 0.26 mmol) in THF (0.5 mL) at –78 °C under argon and stirred for 40 min, then trimethylchlorosilane (40 μL, 0.32 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 40 min and then allowed to warm to rt over 40 min.

The reaction mixture was again cooled to –78 °C and lithium(bistrimethyl)silyl amide (1.0 M, 0.30 mL, 0.30 mmol) was added dropwise, followed by stirring at –78 °C for 30 minutes and then dropwise addition of trimethyl chlorosilane (40 μL, 0.32 mmol). The reaction mixture was stirred at –78 °C for 30 minutes and then warmed to rt.

The reaction mixture was concentrated *in vacuo* and then dissolved in hexane (5 mL) to precipitate out lithium salts, filtered through cotton wool and concentrated *in vacuo* at rt

to obtain 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (**420**, 0.15 g) as a pale yellow oil, contaminated with trimethylsilyl impurities, which was used without further purification.



ν_{max} (neat)/cm^{-1} 2940s (C-H), 2176m (C≡C), 1619s (C=C), 1253s, 1195s; δ_H (500 MHz; C_6D_6) 4.40 (1H, s, C=C*H*), 2.43 (1H, d, *J* 6.3, C=CHC*H*), 2.11 (2H, t, *J* 6.8, SiC≡CC*H*$_2$), 1.95-1.86 (1H, m, 1 of C=CHCHCH$_2$C*H*$_2$), 1.79-1.75 (1H, m, 1 of C=CHCHCH$_2$CH$_2$C*H*$_2$), 1.71-1.65 (1H, m, 1 of C=CHCHCH$_2$C*H*$_2$), 1.63-1.39 (7H, m, 1 of C=CHCHC*H*$_2$, SiC≡CCH$_2$CH$_2$CH$_2$C*H*$_2$, SiC≡CCH$_2$CH$_2$C*H*$_2$ and SiC≡CCH$_2$C*H*$_2$), 1.28-1.22 (1H, m, 1 of C=CHCHC*H*$_2$), 1.01-0.95 (1H, m, 1 of C=CHCHCH$_2$CH$_2$C*H*$_2$), 0.16 (9H, s, OSi(C*H*$_3$)$_3$), CSi(C*H*$_3$)$_3$ obscured by impurities; δ_C (125 MHz; C_6D_6) 152.0 (O*C*=CH), 108.1 (CH$_2$*C*≡CSi(CH$_3$)$_3$), 100.8 (C=*C*H), 84.4 (CH$_2$C≡*C*Si(CH$_3$)$_3$), 61.8 (SiO*C*C), 43.1 (C=CCH*C*H), 34.2 & 25.6 (SiC≡CCH$_2$CH$_2$*C*H$_2$*C*H$_2$), 29.7 (C=CHCHCH$_2$CH$_2$*C*H$_2$), 29.6 (SiC≡CCH$_2$*C*H$_2$), 27.5 (C=CHCH*C*H$_2$), 24.3 (C=CHCHCH$_2$*C*H$_2$), 20.1 (SiC≡C*C*H$_2$), -0.16 (OSi(*C*H$_3$)$_3$), CSi(*C*H$_3$)$_3$ obscured by impurities; *m/z* (CI pos) 335 (MH$^+$, 51%), 319 (100), 261 (45), 173 (50), 73 (65); HRMS calculated for $C_{19}H_{34}OSi_2$ (MH$^+$) 335.2226 Found 335.2227.

Using the procedure of Sugihara *et al.*[29], a solution of 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (**420**, 0.16 g, 0.26 mmol) in 1,2-dichloroethane (1.63 mL) was added to a solution of dicobalt octacarbonyl (0.16 g, 0.48 mmol) in 1,2-dichloroethane (1 mL), under argon at rt. The reaction mixture was stirred at rt for 1 h. *n*-Butyl methyl sulfide (0.11 mL, 0.92 mmol) was added and the reaction mixture heated to reflux overnight.

The reaction mixture was cooled, a solution of *para*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, gradient elution, EtOAc / Hexane 5 : 95 to 50 : 50) to

afford 1-(6-trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one (**419**, 23 mg, 34%) as a colourless oil.

Method 3

Using the procedure of Wu *et al.*[132], lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.28 mL, 0.28 mmol) was added dropwise to a stirred solution of 5-hex-5-ynyl-bicyclo[3.2.0]heptan-6-one (**396**, 50 mg, 0.26 mmol) in THF (0.5 mL) at –78 °C under argon and stirred for 40 min, then trimethylchlorosilane (40 μL, 0.32 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 40 min and then allowed to warm to rt over 40 min.

The reaction mixture was again cooled to –78 °C and lithium(bistrimethyl)silyl amide (1.0 M, 0.30 mL, 0.30 mmol) was added dropwise, followed by stirring at –78 °C for 30 minutes and then dropwise addition of trimethyl chlorosilane (40 μL, 0.32 mmol). The reaction mixture was stirred at –78 °C for 30 minutes and then warmed to rt.

The reaction mixture was concentrated *in vacuo* and then dissolved in hexane (5 mL) to precipitate out lithium salts, filtered through cotton wool and concentrated *in vacuo* at rt to obtain 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (**420**, 0.15 g) as a pale yellow oil, contaminated with trimethylsilyl impurities, which was used without further purification. (see Method 2 for characterisation)

Using the procedure of Sugihara *et al.*[29], a solution of 1-(6-trimethylsilylhex-5-ynyl)-7-trimethylsilyloxybicyclo[3.2.0]hept-6-ene (**420**, 0.15 g, 0.26 mmol) in toluene (1.3 mL) was added to a solution of dicobalt octacarbonyl (0.13 g, 0.39 mmol) in toluene (1 mL), under argon at rt. The reaction mixture was stirred at rt for 1 h and then heated to reflux overnight.

The reaction mixture was cooled, a solution of *para*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in methanol (2 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, gradient elution, EtOAc / Hexane 5 : 95 to 50 : 50) to afford 1-(6-trimethylsilyl-hex-5-ynyl)-bicyclo[3.2.0]heptan-6-one (**419**, 2 mg, 3%) as a colourless oil.

ν_{max} (neat)/cm^{-1} 2940s (sp^3 C-H), 2174m (C≡C), 1772s (C=O), 1249m, 1066m; δ_H (500 MHz; $CDCl_3$) 3.11 (1H, dd, *J* 18.4, 9.5, 1 of OCC*H*$_2$), 2.59-2.54 (1H, m, OCCH$_2$C*H*),

2.43 (1H, dd, *J* 18.5, 4.5, 1 of OCC*H*$_2$), 2.22 (2H, t, *J* 7.0, SiC≡CC*H*$_2$), 2.00 (1H, dd, *J* 12.9, 6.3, 1 of 1 of OCCC*H*$_2$), 1.85-1.77 (3H, m, 1 of OCCH$_2$CHCH$_2$C*H*$_2$, HC≡CCH$_2$CH$_2$CH$_2$C*H*$_2$), 1.73-1.48 (6H, m, 1 of OCCH$_2$CHCH$_2$C*H*$_2$, 1 of OCCH$_2$CHC*H*$_2$, HC≡CCH$_2$C*H*$_2$, HC≡CCH$_2$CH$_2$C*H*$_2$), 1.43-1.35 (2H, m, 1 of OCCC*H*$_2$, 1 of OCCH$_2$CHC*H*$_2$), 0.14 (9H, s, CSi(C*H*$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 218.1 (*C*=O), 107.2 (CH$_2$*C*≡CSi(CH$_3$)$_3$), 84.7 (CH$_2$C≡*C*Si(CH$_3$)$_3$), 75.8 (OC*C*), 49.2 (OC*C*H$_2$), 35.3 (OCC*C*H$_2$),, 33.9 (OCCH$_2$*C*H), 32.7 (HC≡CCH$_2$CH$_2$CH$_2$*C*H$_2$), 32.4 (HC≡CCH$_2$CH$_2$*C*H$_2$), 28.9 (SiC≡CCH$_2$*C*H$_2$), 25.0 (OCCH$_2$CHCH$_2$*C*H$_2$), 24.7 (OCCH$_2$CH*C*H$_2$), 19.6 (SiC≡*C*CH$_2$), 0.13 (Si(*C*H$_3$)$_3$); *m/z* (CI pos) 263 (MH^+, 35%), 247 (39), 173 (26), 131 (30), 83 (50), 73 (100); HRMS calculated for $C_{16}H_{27}OSi$ (MH^+) 263.1831 Found 263.1832.

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